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Remarks:
This application was filed on 21-01-2011 as a divisional application to the application mentioned under INID code 62.

(54) Microrna fingerprints during human megakaryocytopoiesis

(57) The present invention provides novel methods and compositions for the diagnosis, prognosis and treatment of cancer and myeloproliferative disorders. The invention also provides methods of identifying anti-cancer agents.

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Description

CROSS-REFERENCE TO RELATED APPLICATIONS

[0001] This application claims the benefit of United States Provisional Application No. 60/743,585, filed March 20, 2006, the disclosure of which is incorporated herein by reference.

STATEMENT REGARDING FEDERALLY SPONSORED RESEARCH

[0002] The invention was supported, in whole or in part, by National Institutes of Health Program Project Grants PO1CA76259, PO1CA16058, PO1GA81534 and PO1CA16672. The Government has certain rights in the invention.

BACKGROUND OF THE INVENTION

[0003] MicroRNAs (miRNAs) are a small non-coding family of 19-25 nucleotide RNAs that regulate gene expression by targeting messenger RNAs (mRNA) in a sequence specific manner, inducing translational repression or mRNA degradation depending on the degree of complementarity between miRNAs and their targets (Bartel, D.P. (2004) Cell 116, 281-297;' Ambros, V. (2004) Nature 431, 350-355). Many miRNAs are conserved in sequence between distantly related organisms, suggesting that these molecules participate in essential processes. Indeed, miRNAs are involved in the regulation of gene expression during development (Xu, P., et al. (2003) Curr. Biol. 13, 790-795), cell proliferation (Xu, P., et al. (2003) Curr. Biol. 13, 790-795), apoptosis (Cheng, A.M., et al. (2005) Nucl. Acids Res. 33, 1290-1297), glucose metabolism (Poy, M.N., et al. (2004) Nature 432, 226-230), stress resistance (Dresios, J., et al. (2005) Proc. Natl. Acad. Sci. USA 102, 1865-1870) and cancer (Calin, G.A, et al. (2002) Proc. Natl. Acad. Sci. USA 99, 1554-15529; Calin, G.A., et al. (2004) Proc. Natl. Acad. Sci. USA 101, 11755-11760; He, L., et al. (2005) Nature 435, 828-833; and Lu, J., et al. (2005) Nature 435:834-838).

[0004] There is also strong evidence that miRNAs play a role in mammalian hematopoiesis. In mice, miR-181, miR-223 and miR-142 are differentially expressed in hematopoietic tissues, and their expression is regulated during hematopoiesis and lineage commitment (Chen, C.Z., et al. (2004) Science 303, 83-86). The ectopic expression of miR-181 in murine hematopoietic progenitor cells led to proliferation in the B-cell compartment (Chen, C.Z., et al. (2004) Science 303, 83-86). Systematic miRNA gene profiling in cells of the murine hematopoietic system revealed different miRNA expression patterns in the hematopoietic system compared with neuronal tissues, and identified individual miRNA expression changes that occur during cell differentiation (Monticelli, S., et al. (2005) Genome Biology 6, R71). A recent study has identified down-modulation of miR-221 and miR-222 in human erythropoietic cultures of $CD34^+$ cord blood progenitor cells (Felli, N., et al. (2005) Proc. Natl. Acad. Sci. USA. 102, 18081-18086). These miRNAs were found to target the oncogene c-Kit. Further functional studies indicated that the decline of these two miRNAs in erythropoietic cultures unblocks Kit protein production at the translational level leading to expansion of early erythroid cells (Felli, N., et al. (2005) Proc. Natl. Acad. Sci. USA. 102, 18081-18086). In line with the hypothesis of miRNAs regulating cell differentiation, miR-223 was found to be a key member of a regulatory circuit involving C/EBPa and NFI-A, which controls granulocytic differentiation in *all-trans* retinoic acid-treated acute promyelocytic leukemic cell lines (Fazi, F., et al. (2005) Cell 123, 819-831).

[0005] miRNAs have also been found deregulated in hematopoietic malignancies. Indeed,the first report linking miRNAs and cancer involved the deletion and down regulation of the miR-15a and miR-16-1 cluster, located at chromosome 13q14.3, a commonly-deleted region in chronic lymphocytic leukemia (Calin, G.A, et al. (2002) Proc. Natl. Acad. Sci. USA 99,1554-15529). High expression of miR-155 and host gene BIC was also reported in B-cell lymphomas (Metzler M., et al. (2004) Genes Chromosomes and Cancer 39; 167-169). More recently it was shown that the miR-17-92 cluster, which is located in a genomic region of amplification in lymphomas, is overexpressed in human B-cell lymphomas and the enforced expression of this cluster acted in concert with c-MYC expression to accelerate tumor development in a mouse B cell lymphoma model (He, L., et al. (2005) Nature 435, 828-833). These observations indicate that miRNAs are important regulators of hematopoiesis and can be involved in malignant transformation.

[0006] Platelets play an essential role in hemostasis and thrombosis. They are produced from in large numbers from their parent cells, bone marrow megakaryocytes, and arise from fragmentation of the cytoplasm. Only recently has the molecular basis of what may turn out to be a large family of related disorders affecting platelet production started to be defined. If the level of circulating platelets drops below a certain number (thrombocytopenia), the patient runs the risk of catastrophic hemorrhage. Patients with cancer who have received chemotherapy or bone marrow transplants usually have thrombocytopenia, and the slow recovery of platelet count in these patients has been a concern. The demand for platelet units for transfusion has been steadily increasing primarily because of the need to maintain a certain platelet level in such patients with cancer or those undergoing major cardiac surgery.

[0007] Identification of microRNAs that are differentially-expressed in cancer cells (e.g., leukemia cells) may help

pinpoint specific miRNAs that are involved in cancer and other disorders (e.g., platelet disorders). Furthermore, the identification of putative targets of these miRNAs may help to unravel their pathogenic role. In particular, discovering the patterns and sequence of miRNA expression during hematopoietic differentiation may provide insights about the functional roles of these tiny non-coding genes in normal and malignant hematopoiesis.

[0008] There is a need for novel methods and compositions for the diagnosis, prognosis and treatment of cancer, myeloproliferative disorders and platelet disorders (e.g., inherited platelet disorders).

SUMMARY OF THE INVENTION

[0009] The present invention is based, in part, on the identification of specific miRNAs that are involved in megakaryocytic differentiation and/or have altered expression levels in cancerous cells (e.g., in acute megakaryoblastic leukemia (AMKL cell lines)). In the present study, the miRNA gene expression in human megakaryocyte cultures from bone marrow $CD34^+$ progenitors and acute megakaryoblastic leukemia cell lines was investigated. The results of this analysis indicate that several miRNAs are downregulated during normal megakaryocytic differentiation. The results further demonstrate that these miRNAs target genes involved in megakaryocytopoiesis, while others are over expressed in cancer cells.

[0010] Accordingly, the invention encompasses methods of diagnosing or prognosticating cancer and/or a myeloproliferative disorder in a subject (e.g., a human). According to the methods of the invention, the level of at least one miR gene product in a test sample from the subject is compared to the level of a corresponding miR gene product in a control sample. An alteration (e.g., an increase, a decrease) in the level of the miR gene product in the test sample, relative to the level of a corresponding miR gene product in the control sample, is indicative of the subject either having, or being at risk for developing, cancer and/or a myeloproliferative disorder. In one embodiment, the level of the miR gene product in the test sample from the subject is greater than that of the control. In another embodiment, the at least one miR gene product is selected from the group consisting of miR-101, miR-126, miR-99a, miR-99-prec, miR-106, miR-339, miR-99b, miR-149, miR-33, miR-135 and miR-20. In still another embodiment, the at least one miR gene product is selected from the group consisting of miR-101, miR-126, miR-106, miR-20 and miR-135. In yet another embodiment, the at least one miR gene product is selected from the group consisting of miR-106, miR-20 and miR-135. In particular embodiments, the cancer that is diagnosed or prognosticated is a leukemia (e.g., acute myeloid leukemia (e.g., acute megakaryoblastic leukemia)) or multiple myeloma. In other embodiments, the myeloproliferative disorder is selected from the group consisting of essential thrombocytemia (ET), polycythemia vera (PV), myelodisplasia, myelofibrosis (e.g., agnogenic myeloid metaplasia (AMM) (also referred to as idiopathic myelofibrosis)) and chronic myelogenous leukemia (CML).

[0011] In another embodiment, the invention is a method of treating a cancer and/or a myeloproliferative disorder in a subject (e.g., a human). In the method, an effective amount of a compound for inhibiting expression of at least one miR gene product selected from the group consisting of miR-101, miR-126, miR-99a, miR-99-prec, miR-106, miR-339, miR-99b, miR-149, miR-33, miR-135 and miR-20 is administered to the subject. In one embodiment, the compound for inhibiting expression of at least one miR gene product inhibits expression of a miR gene product selected from the group consisting of miR-101, miR-126, miR-106, miR-20 and miR-135. In another embodiment the compound for inhibiting expression of at least one miR gene product inhibits expression of a miR gene product selected from the group consisting of miR-106, miR-20 and miR-135. In particular embodiments, the cancer that is treated is a leukemia (e.g., acute myeloid leukemia (e.g., acute megakaryoblastic leukemia)) or multiple myeloma. In other embodiments, the myeloproliferative disorder is selected from the group consisting of essential thrombocytemia (ET), polycythemia vera (PV), myelodisplasia, myelofibrosis (e.g., agnogenic myeloid metaplasia (AMM)) and chronic myelogenous leukemia (CML).

[0012] In another embodiment, the invention is a method of treating a cancer and/or a myeloproliferative disorder associated with overexpression of a MAFB gene product in a subject (e.g., a human). In the method, an effective amount of at least one miR gene product or a variant or biologically-active fragment thereof, which binds to, and decreases expression of, the MAFB gene product, is administered to the subject. In one embodiment, the at least one miR gene product, variant or biologically-active fragment thereof comprises a nucleotide sequence that is complementary to a nucleotide sequence in the MAFB gene product. In another embodiment, the at least one miR gene product is miR-130a or a variant or biologically-active fragment thereof. Cancers and myeloproliferative disorders suitable for treatment using this method include, for example, those described herein.

[0013] In another embodiment, the invention is a method of treating a cancer and/or a myeloproliferative disorder associated with overexpression of a HOXA1 gene product in a subject (e.g., a human). In the method, an effective amount of at least one miR gene product or a variant or biologically-active fragment thereof, which binds to, and decreases expression of, the HOXA1 gene product, is administered to the subject. In one embodiment, the at least one miR gene product, variant or biologically-active fragment thereof comprises a nucleotide sequence that is complementary to a nucleotide sequence in the HOXA1 gene product. In another embodiment, the at least one miR gene product is miR-10a or a variant or biologically-active fragment thereof. Cancers and myeloproliferative disorders suitable for treatment using this method include, for example, those described herein.

[0014] In one embodiment, the invention is a method of determining and/or predicting megakaryocytic differentiation. In this method, the level of at least one miR gene product in a sample (e.g., a sample from a subject (e.g., a human)) comprising megakaryocyte progeny and/or megakaryocytes is determined. That level is compared to the level of the corresponding miR gene product in a control. An alteration in the level of the at least one miR gene product in the sample, relative to that of the control, is indicative of megakaryocytic differentiation. In one embodiment, the alteration is a decrease in the level of the at least one miR gene product in the sample. In another embodiment, the at least one miR gene product is selected from the group consisting of miR-10a, miR-126, miR-106, miR-010b, miR-130a, miR-130a-prec, miR-124a, miR-032-prec, miR-101, miR-30c, miR-213, nniR-132-prec, miR-150, miR-020, miR-339, let-7a, let-7d, miR-181c, miR-181b and miR-017. In still another embodiment, the at least one miR gene product is selected from the group consisting of miR-10a, miR-10b, miR-30c, miR-106, miR-126, miR-130a, miR-132, and miR-143.

[0015] The invention further provides pharmaceutical compositions for treating cancer and/or a myeloproliferative disorder. In one embodiment, the pharmaceutical compositions of the invention comprise at least one miR expression-inhibition compound and a pharmaceutically-acceptable carrier. In a particular embodiment, the at least one miR expression-inhibition compound is specific for a miR gene product whose expression is greater in cancer cells (e.g., acute megakaryoblastic leukemia (AMKL) cells) than control cells (i.e., it is upregulated). In one embodiment, the miR expression-inhibition compound is specific for one or more miR gene products selected from the group consisting of miR-101, miR-126, mik-99a, miR-99-prec, miR-106, miR-339, miR-99b, miR-149, miR-33, miR-135 and miR-20. In another embodiment, the miR expression-inhibition compound is specific for one or more miR gene products selected from the group consisting of miR-101, miR-126, miR-106, miR-20, and miR-135. In still another embodiment, the miR expression-inhibition compound is specific for one or more miR gene products selected from the group consisting of miR-106, miR-20 and miR-135. In yet another embodiment, the pharmaceutical composition further comprises at least one anti-cancer agent.

[0016] In one embodiment, the invention is a pharmaceutical composition for treating a cancer associated with overexpression of a MAFB gene product and/or a myeloproliferative disorder associated with overexpression of a MAFB gene product. Such pharmaceutical compositions comprise an effective amount of at least one miR gene product and a pharmaceutically-acceptable carrier, wherein the at least one miR gene product binds to, and decreases expression of, the MAFB gene product. In another embodiment, the at least one miR gene product comprises a nucleotide sequence that is complementary to a nucleotide sequence in the MAFB gene product. In still another embodiment, the at least one miR gene product is miR-130a or a variant or biologically-active fragment thereof. In yet another embodiment, the pharmaceutical composition further comprises at least one anti-cancer agent.

[0017] In one embodiment, the invention is a pharmaceutical composition for treating a cancer associated with overexpression of a HOXA1 gene product and/or a myeloproliferative disorder associated with overexpression of a HOXA1 gene product. Such pharmaceutical compositions comprise an effective amount of at least one miR gene product and a pharmaceutically-acceptable carrier, wherein the at least one miR gene product binds to, and decreases expression of, the HOXA1 gene product. In another embodiment, the at least one miR gene product comprises a nucleotide sequence that is complementary to a nucleotide sequence in the HOXA1 gene product. In still another embodiment, the at least one miR gene product is miR-10a or a variant or biologically-active fragment thereof. In yet another embodiment, the pharmaceutical composition further comprises at least one anti-cancer agent.

[0018] Various objects and advantages of this invention will become apparent to those skilled in the art from the following detailed description of the preferred embodiment, when read in light of the accompanying drawings.

BRIEF DESCRIPTION OF THE DRAWING

[0019] The patent or application file contains at least one drawing executed in color. Copies of this patent or patent application publication with color drawing(s) will be provided by the Office upon request and payment of the necessary fee.

[0020] FIGS. 1A-1D depict Northern Blots and Real Time miRNA-PCR results, which validate microRNA chip data in CD34 progenitor differentiation experiments.

[0021] FIG. 1A depicts Northern Blots for miR-130a, miR-10a and miR-223. A loading RNA control was performed with U6.

[0022] FIG. 1B is a graph depicting RT-miRNA-PCR for miR-10a, miR-106, miR-126 and miR-130a. miRNA expression is presented as fold difference with respect to $CD34^+$ cells before culture.

[0023] FIG. 1C is a graph depicting temporal expression of miR-223 by microarray.

[0024] FIG. 1D is a graph depicting temporal expression of miR-15-1 and miR-16-1 by RT-miRNA PCR.

[0025] FIGS. 2A-2C demonstrate that MAFB is a target of miR-130a.

[0026] FIG. 2A depicts MAFB mRNA and protein expression data in $CD34^+$ progenitors induced to megakaryocytic differentiation. β-Actin was used for RT-PCR and Western blot loading controls.

[0027] FIG. 2B is a graph depicting relative repression of luciferase activity in MEG01 cells co-transfected with miR-10a and PGL3 3'UTRMAFB, miR-10a with PGL3 3'UTR, miR-10a seed match mutated and scramble with mutated, and

wild type 3'UTR MAFB.

[0028] FIG. 2C depicts Western blots of MAFB total protein lysates in K562 cells transfected with miR-130a and scramble.

[0029] FIGS. 3A-3G demonstrate that MiR-10a downregulates HOXA1 by mediating RNA cleavage.

[0030] FIG. 3A is a graph depicting RT-PCR results for HOXA1 gene expression in differentiated megakaryocytes (Relative amount of transcript with respect to $CD34^+$ progenitors at baseline).

[0031] FIG. 3B is a Western blot showing hoxa1 protein expression in differentiated megakaryocytes.

[0032] FIG. 3C is a graph depicting relative repression of luciferase activity of HOXA1 3' UTR cloned PGL3 reporter plasmid when co-transfected with miR-10a and control scramble.

[0033] FIG. 3D is a schematic showing complementarity between miR-10a and the HOXA1 3'UTR as predicted by PICTAR.

[0034] FIG. 3E depicts RT-PCR results for miR-10a gene expression in scramble and miR-10a precursor transfected K562 cells.

[0035] FIG. 3F depicts RT-PCR results for HOXA1 gene expression in scramble and miR-10a precursor transfected K562 cells.

[0036] FIG. 3G is a Western blot showing HOXA1 expression in K562 cells transfected with control scramble and precursor miR-10a.

[0037] FIGS. 4A and 4B. show phenotypic characterization results of *in vitro*-differentiated $CD34^+$ progenitors.

[0038] FIG. 4A depicts May-Giemsa stains that were performed on cytospin preparations from $CD34^+$ progenitors in culture at different days of culture (day 6, day 10, day 12 and day 14). At day 4, most of the cells were immature, as evidenced by the high nucleous:cytoplasmic ratio. Larger and multinuclear cells were observed by day 10. At day 14, predominantly larger, polyploid cells with long cytoplasmic processes and numerous membrane blebs with invaginations and vacuoles (original magnification 400X) were observed.

[0039] FIG. 4B depicts FACS analysis of CD34 in vitro-differentiated megakaryocytes. The membrane phenotype of $CD34^+$ progenitor cells that are grown in culture is shown. Cells were harvested at days 10 (D+10), 14 (D+14) and 16 (D+16) and were analyzed by single fluorescent labeling using an anti-CD41 antibody, an anti-CD61a antibody, an anti-CD42a antibody and their respective isotype monoclonal antibodies (D + 10 isotype; D + 14 isotype; D + 16 isotype). Double labeling was performed with anti-CD41a and CD61b monoclonal Abs at day 14 only.

[0040] FIG. 5 is a graph depicting RT-PCR expression results for miR-20 and miR-17 in differentiated megakaryocytes. The results are presented as fold difference with respect to $CD34^+$ cells at baseline after normalization with 18S and delta Ct calculations.

[0041] FIG. 6A is a graph depicting temporal expression of miR-16-1 during megakaryocytic differentiation. The absolute expression value of miR-16-1 was determined by a per-chip median normalization.

[0042] FIG. 6B is a graph depicting temporal expression of miR-142 during megakaryocytic differentiation. The absolute expression value of miR-142 was determined by a per-chip median normalization.

[0043] FIG. 6C is a graph depicting temporal expression of miR-181b during megakaryocytic differentiation. The absolute expression value of miR-181b was determined by a per-chip median normalization.

[0044] FIG. 7 is a Northern Blot of total RNA obtained from K562 cells transfected with *miR-130a* precursor and scramble sequences hybridized with the probe for miR-130a. An RNA loading control was performed using U6 hybridization.

[0045] FIG. 8 is a schematic depicting microRNAs that are located in the HOXA, HOXB, HOXC and HOXD gene clusters.

[0046] FIG. 9A is a graph depicting HOXB4 gene expression in differentiated megakaryocytes. RT-PCR results for HOXB4 are shown as fold difference in the expression level with respect to $CD34^+$ progenitors at baseline (before culture).

[0047] FIG. 9B is a graph depicting HOXB5 gene expression in differentiated megakaryocytes. RT-PCR results for HOXB5 are shown as fold difference in the expression levels with respect to $CD34^+$ progenitors at baseline (before culture).

[0048] FIG. 10 is a graph depicting microRNA expression in acute megakaryoblastic cell lines by RT-PCR. Results are expressed as fold difference with respect to CD34-differentiated megakaryocytes after normalization with 18S and delta Ct calculations.

DETAILED DESCRIPTION OF THE PREFERRED EMBODIMENT

[0049] The present invention is based, in part, on the identification of specific microRNAs (miRNAs) that are involved in megakaryocytic differentiation and/or have altered expression levels in cancerous cells (e.g., in acute megakaryoblastic leukemia (AMKL cell lines)). The invention is further based, in part, on association of these miRNAs with particular diagnostic, prognostic and therapeutic features. As described and exemplified herein:

[0050] i) particular miRNA are downregulated during megakaryocytic differentiation;

[0051] ii) the transcription factor MAFB is a target for miR-130a;

[0052] iii) miR-10a expression parallels that of HOXB gene expression;

[0053] iv) miR-10a downregulates HOXA1 expression; and

[0054] v) particular miRNA are upregulated in cancerous cells (e.g., acute megakaryoblastic leukemia (AMKL) cells).

[0055] As used herein interchangeably, a "miR gene product," "microRNA," "miR," *"miR"* or "miRNA" refers to the unprocessed or processed RNA transcript from a miR gene. As the miR gene products are not translated into protein, the term "miR gene products" does not include proteins. The unprocessed miR gene transcript is also called a "miR precursor," and typically comprises an RNA transcript of about 70-100 nucleotides in length. The miR precursor can be processed by digestion with an RNAse (for example, Dicer, Argonaut, RNAse III (e.g., *E. coli* RNAse III)) into an active 19-25 nucleotide RNA molecule. This active 19-25 nucleotide RNA molecule is also called the "processed" miR gene transcript or "mature" miRNA.

[0056] The active 19-25 nucleotide RNA molecule can be obtained from, the miR precursor through natural processing routes (e.g., using intact cells or cell lysates) or by synthetic processing routes (e.g., using isolated processing enzymes, such as isolated Dicer, Argonaut, or RNAse III). It is understood that the active 19-25 nucleotide RNA molecule can also be produced directly by biological or chemical synthesis, without having to be processed from the miR precursor. When a microRNA is referred to herein by name, the name corresponds to both the precursor and mature forms, unless otherwise indicated.

[0057] Tables 1a and 1b depict the nucleotide sequences of particular precursor and mature human microRNAs.

[0058]

Table 1a: Human microRNA Precursor Sequences.

Precursor Name	Sequence (5' To 3')*	SEQ ID NO.
let-7a-1	CACUGUGGGAUGAGGUAGUAGGUUGUAUAGUUUUA GGGUCACACCCACCACUGGGAGAUAACUAUACAAU CUACUGUCUUUCCUAACGUG	1
let-7a-2	AGGUUGAGGUAGUAGGUUGUAUAGUUUAGAAUUAC AUCAAGGGAGAUAACUGUACAGCCUCCUAGCUUUC CU	2
let-7a-3	GGGUGAGGUAGUAGGUUGUAUAGUUUGGGGCUCUG CCCUGCUAUGGGAUAACUAUACAAUCUACUGUCUU UCCU	3
let-7a-4	GUGACUGCAUGCUCCCAGGUUGAGGUAGUAGGUUG UAUAGUUUAGAAUUACACAAGGGAGAUAACUGUAC AGCCUCCUAGCUUUCCUUGGGUCUUGCACUAAACA AC	4
let-7b	GGCGGGGUGAGGUAGUAGGUUGUGUGGUUUCAGGG CAGUGAUGUUGCCCCUCGGAAGAUAACUAUACAAC CUACUGCCUUCCCUG	5
let-7c	GCAUCCGGGUUGAGGUAGUAGGUUGUAUGGUUUAG AGUUACACCCUGGGAGUUAACUGUACAACCUUCUA GCUUUCCUUGGAGC	6
let-7d	CCUAGGAAGAGGUAGUAGGUUGCAUAGUUUUAGGG CAGGGAUUUUGCCCACAAGGAGGUAACUAUACGAC CUGCUGCCUUUCUUAGG	7
let-7d-v1	CUAGGAAGAGGUAGUAGUUUGCAUAGUUUUAGGGC AAAGAUUUUGCCCACAAGUAGUUAGCUAUACGACC UGCAGCCUUUUGUAG	8
let-7d-v2	CUGGCUGAGGUAGUAGUUUGUGCUGUUGGUCGGGU UGUGACAUUGCCCGCUGUGGAGAUAACUGCGCAAG CUACUGCCUUGCUAG	9

(continued)

Precursor Name	Sequence (5' To 3')*	SEQ ID NO.
let-7e	CCCGGGCUGAGGUAGGAGGUUGUAUAGUUGAGGAG GACACCCAAGGAGAUCACUAUACGGCCUCCUAGCUU UCCCCAGG	10
let-7f-1	UCAGAGUGAGGUAGUAGAUUGUAUAGUUGUGGGGU AGUGAUUUUACCCUGUUCAGGAGAUAACUAUACAA UCUAUUGCCUUCCCUGA	11
let-7f-2-1	CUGUGGGAUGAGGUAGUAGAUUGUAUAGUUGUGGG GUAGUGAUUUUACCCUGUUCAGGAGAUAACUAUAC AAUCUAUUGCCUUCCCUGA	12
let-7f-2-2	CUGUGGGAUGAGGUAGUAGAUUGUAUAGUUUUAGG GUCAUACCCCAUCUUGGAGAUAACUAUACAGUCUA CUGUCUUUCCCACGG	13
let-7g	UUGCCUGAUUCCAGGCUGAGGUAGUAGUUUGUACA GUUUGAGGGUCUAUGAUACCACCCGGUACAGGAGA UAACUGUACAGGCCACUGCCUUGCCAGGAACAGCGC GC	14
let-7i	CUGGCUGAGGUAGUAGUUUGUGCUGUUGGUCGGGU UGUGACAUUGCCCGCUGUGGAGAUAACUGCGCAAG CUACUGCCUUGCUAG	15
miR-1b-1-1	ACCUACUCAGAGUACAUACUUCUUUAUGUACCCAU AUGAACAUACAAUGCUAUGGAAUGUAAAGAAGUAU GUAUUUUUGGUAGGC	16
miR-1b-1-2	CAGCUAACAACUUAGUAAUACCUACUCAGAGUACA UACUUCUUUAUGUACCCAUAUGAACAUACAAUGCU AUGGAAUGUAAAGAAGUAUGUAUUUUUGGUAGGCA AUA	17
miR-1b-2	GCCUGCUUGGGAAACAUACUUCUUUAUAUGCCCAU AUGGACCUGCUAAGCUAUGGAAUGUAAAGAAGUAU GUAUCUCAGGCCGGG	18
miR-1b	UGGGAAACAUACUUCUUUAUAUGCCCAUAUGGACC UGCUAAGCUAUGGAAUGUAAAGAAGUAUGUAUCUC A	19
miR-1d	ACCUACUCAGAGUACAUACUUCUUUAUGUACCCAU AUGAACAUACAAUGCUAUGGAAUGUAAAGAAGUAU GUAUUUUUGGUAGGC	20
miR-7-1a	UGGAUGUUGGCCUAGUUCUGUGUGGAAGACUAGUG AUUUUGUUGUUUUUAGAUAACUAAAUCGACAACAA AUCACAGUCUGCCAUAUGGCACAGGCCAUGCCUCUA CA	21
m*iR-7-1b*	UUGGAUGUUGGCCUAGUUCUGUGUGGAAGACUAGU GAUUUUGUUGUUUUUAGAUAACUAAAUCGACAACA AAUCACAGUCUGCCAUAUGGCACAGGCCAUGCCUCU ACAG	22

(continued)

Precursor Name	Sequence (5' To 3')*	SEQ ID NO.
miR-7-2	CUGGAUACAGAGUGGACCGGCUGGCCCCAUCUGGAAGACUAGUGAUUUUGUUGUUGUCUUACUGCGCUCAACAACAAAUCCCAGUCUACCUAAUGGUGCCAGCCAUCGCA	23
miR-7-3	AGAUUAGAGUGGCUGUGGUCUAGUGCUGUGUGGAAGACUAGUGAUUUUGUUGUUCUGAUGUACUACGACAACAAGUCACAGCCGGCCUCAUAGCGCAGACUCCCUUCGAC	24
miR-9-1	CGGGGUUGGUUGUUAUCUUUGGUUAUCUAGCUGUAUGAGUGGGUGUGGAGUCUUCAUAAAGCUAGAUAACCGAAAGUAAAAAUAACCCCA	25
miR-9-2	GGAAGCGAGUUGUUAUCUUUGGUUAUCUAGCUGUAUGAGUGUAUUGGUCUUCAUAAAGCUAGAUAACCGAAAGUAAAAACUCCUUCA	26
miR-9-3	GGAGGCCCGUUUCUCUCUUUGGUUAUCUAGCUGUAUGAGUGCCACAGAGCCGUCAUAAAGCUAGAUAACCGAAAGUAGAAAUGAUUCUCA	27
miR-10a	GAUCUGUCUGUCUUCUGUAUAUACCCUGUAGAUCCGAAUUUGUGUAAGGAAUUUUGUGGUCACAAAUUCGUAUCUAGGGGAAUAUGUAGUUGACAUAAACACUCCGCUCU	28
miR-10b	CCAGAGGUUGUAACGUUGUCUAUAUAUACCCUGUAGAACCGAAUUUGUGUGGUAUCCGUAUAGUCACAGAUUCGAUUCUAGGGGAAUAUAUGGUCGAUGCAAAAACUUCA	29
miR-15a-2	GCGCGAAUGUGUGUUUAAAAAAAAUAAAACCUUGGAGUAAAGUAGCAGCACAUAAUGGUUUGUGGAUUUUGAAAAGGUGCAGGCCAUAUUGUGCUGCCUCAAAAAUAC	30
miR-15a	CCUUGGAGUAAAGUAGCAGCACAUAAUGGUUUGUGGAUUUUGAAAAGGUGCAGGCCAUAUUGUGCUGCCUCAAAAAUACAAGG	31
miR-15b-1	CUGUAGCAGCACAUCAUGGUUUACAUGCUACAGUCAAGAUGCGAAUCAUUAUUUGCUGCUCUAG	32
miR-15b-2	UUGAGGCCUUAAAGUACUGUAGCAGCACAUCAUGGUUUACAUGCUACAGUCAAGAUGCGAAUCAUUAUUUGCUGCUCUAGAAAUUUAAGGAAAUUCAU	33
miR-16-1	GUCAGCAGUGCCUUAGCAGCACGUAAAUAUUGGCGUUAAGAUUCUAAAAUUAUCUCCAGUAUUAACUGUGCUGCUGAAGUAAGGUUGAC	34
miR-16-2	GUUCCACUCUAGCAGCACGUAAAUAUUGGCGUAGUGAAAUAUAUAUUAAACACCAAUAUUACUGUGCUGCUUUAGUGUGAC	35

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Precursor Name	Sequence (5' To 3')*	SEQ ID NO.
miR-16-13	GCAGUGCCUUAGCAGCACGUAAAUAUUGGCGUUAA GAUUCUAAAAUUAUCUCCAGUAUUAACUGUGCUGC UGAAGUAAGGU	36
miR-17	GUCAGAAUAAUGUCAAAGUGCUUACAGUGCAGGUA GUGAUAUGUGCAUCUACUGCAGUGAAGGCACUUGU AGCAUUAUGGUGAC	37
miR-18	UGUUCUAAGGUGCAUCUAGUGCAGAUAGUGAAGUA GAUUAGCAUCUACUGCCCUAAGUGCUCCUUCUGGC A	38
miR-18-13	UUUUUGUUCUAAGGUGCAUCUAGUGCAGAUAGUGA AGUAGAUUAGCAUCUACUGCCCUAAGUGCUCCUUC UGGCAUAAGAA	39
miR-19a	GCAGUCCUCUGUUAGUUUUGCAUAGUUGCACUACA AGAAGAAUGUAGUUGUGCAAAUCUAUGCAAAACUG AUGGUGGCCUGC	40
miR-19a-13	CAGUCCUCUGUUAGUUUUGCAUAGUUGCACUACAA GAAGAAUGUAGUUGUGCAAAUCUAUGCAAAACUGA UGGUGGCCUG	41
miR-19b-1	CACUGUUCUAUGGUUAGUUUUGCAGGUUUGCAUCC AGCUGUGUGAUAUUCUGCUGUGCAAAUCCAUGCAA AACUGACUGUGGUAGUG	42
miR-19b-2	ACAUUGCUACUUACAAUUAGUUUUGCAGGUUUGCA UUUCAGCGUAUAUAUGUAUAUGUGGCUGUGCAAAU CCAUGCAAAACUGAUUGUGAUAAUGU	43
miR-19b-13	UUCUAUGGUUAGUUUUGCAGGUUUGCAUCCAGCUG UGUGAUAUUCUGCUGUGCAAAUCCAUGCAAAACUG ACUGUGGUAG	44
miR-19b-X	UUACAAUUAGUUUUGCAGGUUUGCAUUUCAGCGUA UAUAUGUAUAUGUGGCUGUGCAAAUCCAUGCAAAA CUGAUUGUGAU	45
miR-20 miR-20a)	GUAGCACUAAAGUGCUUAUAGUGCAGGUAGUGUUU AGUUAUCUACUGCAUUAUGAGCACUUAAAGUACUG C	46
miR-21	UGUCGGGUAGCUUAUCAGACUGAUGUUGACUGUUG AAUCUCAUGGCAACACCAGUCGAUGGGCUGUCUGA CA	47
miR-21-17	ACCUUGUCGGGUAGCUUAUCAGACUGAUGUUGACU GUUGAAUCUCAUGGCAACACCAGUCGAUGGGCUGU CUGACAUUUUG	48
miR-22	GGCUGAGCCGCAGUAGUUCUUCAGUGGCAAGCUUU AUGUCCUGACCCAGCUAAAGCUGCCAGUUGAAGAA CUGUUGCCCUCUGCC	49

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Precursor Name	Sequence (5' To 3')*	SEQ ID NO.
miR-23a	GGCCGGCUGGGGUUCCUGGGGAUGGGAUUUGCUUC CUGUCACAAAUCACAUUGCCAGGGAUUUCCAACCG ACC	50
miR-23b	CUCAGGUGCUCUGGCUGCUUGGGUUCCUGGCAUGC UGAUUUGUGACUUAAGAUUAAAAUCACAUUGCCAG GGAUUACCACGCAACCACGACCUUGGC	51
miR-23-19	CCACGGCCGGCUGGGGUUCCUGGGGAUGGGAUUUG CUUCCUGUCACAAAUCACAUUGCCAGGGAUUUCCA ACCGACCCUGA	52
miR-24-1	CUCCGGUGCCUACUGAGCUGAUAUCAGUUCUCAUU UUACACACUGGCUCAGUUCAGCAGGAACAGGAG	53
miR-24-2	CUCUGCCUCCCGUGCCUACUGAGCUGAAACACAGUU GGUUUGUGUACACUGGCUCAGUUCAGCAGGAACAG GG	54
miR-24-19	CCCUGGGCUCUGCCUCCCGUGCCUACUGAGCUGAAA CACAGUUGGUUUGUGUACACUGGCUCAGUUCAGCA GGAACAGGGG	55
miR-24-9	CCCUCCGGUGCCUACUGAGCUGAUAUCAGUUCUCAU UUUACACACUGGCUCAGUUCAGCAGGAACAGCAUC	56
miR-25	GGCCAGUGUUGAGAGGCGGAGACUUGGGCAAUUGC UGGACGCUGCCCUGGGCAUUGCACUUGUCUCGGUC UGACAGUGCCGGCC	57
miR-26a	AGGCCGUGGCCUCGUUCAAGUAAUCCAGGAUAGGC UGUGCAGGUCCCAAUGGCCUAUCUUGGUUACUUGC ACGGGGACGCGGGCCU	58
miR-26a-1	GUGGCCUCGUUCAAGUAAUCCAGGAUAGGCUGUGC AGGUCCCAAUGGGCCUAUUCUUGGUUACUUGCACG GGGACGC	59
miR-26a-2	GGCUGUGGCUGGAUUCAAGUAAUCCAGGAUAGGCU GUUUCCAUCUGUGAGGCCUAUUCUUGAUUACUUGU UUCUGGAGGCAGCU	60
miR-26b	CCGGGACCCAGUUCAAGUAAUUCAGGAUAGGUUGU GUGCUGUCCAGCCUGUUCUCCAUUACUUGGCUCGG GGACCGG	61
miR-27a	CUGAGGAGCAGGGCUUAGCUGCUUGUGAGCAGGGU CCACACCAAGUCGUGUUCACAGUGGCUAAGUUCCGC CCCCCAG	62
miR-27b-1	AGGUGCAGAGCUUAGCUGAUUGGUGAACAGUGAUU GGUUUCCGCUUUGUUCACAGUGGCUAAGUUCUGCA CCU	63
miR-27b-2	ACCUCUCUAACAAGGUGCAGAGCUUAGCUGAUUGG UGAACAGUGAUUGGUUUCCGCUUUGUUCACAGUGG CUAAGUUCUGCACCUGAAGAGAAGGUG	64

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Precursor Name	Sequence (5' To 3')*	SEQ ID NO.
miR-27-19	CCUGAGGAGCAGGGCUUAGCUGCUUGUGAGCAGGG UCCACACCAAGUCGUGUUCACAGUGGCUAAGUUCC GCCCCCCAGG	65
miR-28	GGUCCUUGCCCUCAAGGAGCUCACAGUCUAUUGAG UUACCUUUCUGACUUUCCCACUAGAUUGUGAGCUC CUGGAGGGCAGGCACU	66
miR-29a-2	CCUUCUGUGACCCCUUAGAGGAUGACUGAUUUCUU UUGGUGUUCAGAGUCAAUAUAAUUUUCUAGCACCA UCUGAAAUCGGUUAUAAUGAUUGGGGAAGAGCACC AUG	67
miR-29a	AUGACUGAUUUCUUUUGGUGUUCAGAGUCAAUAUA AUUUUCUAGCACCAUCUGAAAUCGGUUAU	68
miR-29b-1	CUUCAGGAAGCUGGUUUCAUAUGGUGGUUUAGAUU UAAAUAGUGAUUGUCUAGCACCAUUUGAAAUCAGU GUUCUUGGGGG	69
miR-29b-2	CUUCUGGAAGCUGGUUUCACAUGGUGGCUUAGAUU UUUCCAUCUUUGUAUCUAGCACCAUUUGAAAUCAG UGUUUUAGGAG	70
m*iR-29c*	ACCACUGGCCCAUCUCUUACACAGGCUGACCGAUUU CUCCUGGUGUUCAGAGUCUGUUUUUGUCUAGCACC AUUUGAAAUCGGUUAUGAUGUAGGGGGAAAAGCAG CAGC	71
m*iR-30a*	GCGACUGUAAACAUCCUCGACUGGAAGCUGUGAAG CCACAGAUGGGCUUUCAGUCGGAUGUUUGCAGCUG C	72
miR-30b-1	AUGUAAACAUCCUACACUCAGCUGUAAUACAUGGA UUGGCUGGGAGGUGGAUGUUUACGU	73
miR-30b-2	ACCAAGUUUCAGUUCAUGUAAACAUCCUACACUCA GCUGUAAUACAUGGAUUGGCUGGGAGGUGGAUGUU UACUUCAGCUGACUUGGA	74
miR-30c	AGAUACUGUAAACAUCCUACACUCUCAGCUGUGGA AAGUAAGAAAGCUGGGAGAAGGCUGUUUACUCUUU CU	75
miR-30d	GUUGUUGUAAACAUCCCCGACUGGAAGCUGUAAGA CACAGCUAAGCUUUCAGUCAGAUGUUUGCUGCUAC	76
miR-30e	CUGUAAACAUCCUUGACUGGAAGCUGUAAGGUGUU CAGAGGAGCUUUCAGUCGGAUGUUUACAG	77
miR-31	GGAGAGGAGGCAAGAUGCUGGCAUAGCUGUUGAAC UGGGAACCUGCUAUGCCAACAUAUUGCCAUCUUUC C	78
miR-32	GGAGAUAUUGCACAUUACUAAGUUGCAUGUUGUCA CGGCCUCAAUGCAAUUUAGUGUGUGUGAUAUUUUC	79

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Precursor Name	Sequence (5' To 3')*	SEQ ID NO.
miR-33b	GGGGGCCGAGAGAGGCGGGCGGCCCCGCGGUGCAU UGCUGUUGCAUUGCACGUGUGUGAGGCGGGUGCAG UGCCUCGGCAGUGCAGCCCGGAGCCGGCCCCUGGCA CCAC	80
miR-33b-2	ACCAAGUUUCAGUUCAUGUAAACAUCCUACACUCA GCUGUAAUACAUGGAUUGGCUGGGAGGUGGAUGUU UACUUCAGCUGACUUGGA	81
miR-33	CUGUGGUGCAUUGUAGUUGCAUUGCAUGUUCUGGU GGUACCCAUGCAAUGUUUCCACAGUGCAUCACAG	82
miR-34-a	GGCCAGCUGUGAGUGUUUCUUUGGCAGUGUCUUAG CUGGUUGUUGUGAGCAAUAGUAAGGAAGCAAUCAG CAAGUAUACUGCCCUAGAAGUGCUGCACGUUGUGG GGCCC	83
miR-34-b	GUGCUCGGUUUGUAGGCAGUGUCAUUAGCUGAUUG UACUGUGGUGGUUACAAUCACUAACUCCACUGCCA UCAAAACAAGGCAC	84
miR-34-c	AGUCUAGUUACUAGGCAGUGUAGUUAGCUGAUUGC UAAUAGUACCAAUCACUAACCACACGGCCAGGUAA AAAGAUU	85
miR-91-13	UCAGAAUAAUGUCAAAGUGCUUACAGUGCAGGUAG UGAUAUGUGCAUCUACUGCAGUGAAGGCACUUGUA GCAUUAUGGUGA	86
miR-92-1	CUUUCUACACAGGUUGGGAUCGGUUGCAAUGCUGU GUUUCUGUAUGGUAUUGCACUUGUCCCGGCCUGUU GAGUUUGG	87
miR-92 -2	UCAUCCCUGGGUGGGGAUUUGUUGCAUUACUUGUG UUCUAUAUAAAGUAUUGCACUUGUCCCGGCCUGUG GAAGA	88
miR-93-1 (miR-93-2)	CUGGGGGCUCCAAAGUGCUGUUCGUGCAGGUAGUG UGAUUACCCAACCUACUGCUGAGCUAGCACUUCCCG AGCCCCCGG	89
miR-95-4	AACACAGUGGGCACUCAAUAAAUGUCUGUUGAAUU GAAAUGCGUUACAUUCAACGGGUAUUUAUUGAGCA CCCACUCUGUG	90
miR-96-7	UGGCCGAUUUUGGCACUAGCACAUUUUUGCUUGUG UCUCUCCGCUCUGAGCAAUCAUGUGCAGUGCCAAU AUGGGAAA	91
miR-97-6 (miR-30)*	GUGAGCGACUGUAAACAUCCUCGACUGGAAGCUGU GAAGCCACAGAUGGGCUUUCAGUCGGAUGUUUGCA GCUGCCUACU	92
miR-98	GUGAGGUAGUAAGUUGUAUUGUUGUGGGGUAGGGA UAUUAGGCCCCAAUUAGAAGAUAACUAUACAACUU ACUACUUUCC	93

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Precursor Name	Sequence (5' To 3')*	SEQ ID NO.
miR-99b	GGCACCCACCCGUAGAACCGACCUUGCGGGGCCUUC GCCGCACACAAGCUCGUGUCUGUGGGUCCGUGUC	94
miR-99a	CCCAUUGGCAUAAACCCGUAGAUCCGAUCUUGUGG UGAAGUGGACCGCACAAGCUCGCUUCUAUGGGUCU GUGUCAGUGUG	95
miR-100-1/2	AAGAGAGAAGAUAUUGAGGCCUGUUGCCACAAACC CGUAGAUCCGAACUUGUGGUAUUAGUCCGCACAAG CUUGUAUCUAUAGGUAUGUGUCUGUUAGGCAAUCU CAC	96
miR-100-11	CCUGUUGCCACAAACCCGUAGAUCCGAACUUGUGG UAUUAGUCCGCACAAGCUUGUAUCUAUAGGUAUGU GUCUGUUAGG	97
miR-101-1/2	AGGCUGCCCUGGCUCAGUUAUCACAGUGCUGAUGC UGUCUAUUCUAAAGGUACAGUACUGUGAUAACUGA AGGAUGGCAGCCAUCUUACCUUCCAUCAGAGGAGC CUCAC	98
miR-101	UCAGUUAUCACAGUGCUGAUGCUGUCCAUUCUAAA GGUACAGUACUGUGAUAACUGA	99
miR-101-1	UGCCCUGGCUCAGUUAUCACAGUGCUGAUGCUGUC UAUUCUAAAGGUACAGUACUGUGAUAACUGAAGGA UGGCA	100
m*iR-101-2*	ACUGUCCUUUUUCGGUUAUCAUGGUACCGAUGCUG UAUAUCUGAAAGGUACAGUACUGUGAUAACUGAAG AAUGGUGGU	101
miR-101-9	UGUCCUUUUUCGGUUAUCAUGGUACCGAUGCUGUA UAUCUGAAAGGUACAGUACUGUGAUAACUGAAGAA UGGUG	102
miR-102-1	CUUCUGGAAGCUGGUUUCACAUGGUGGCUUAGAUU UUUCCAUCUUUGUAUCUAGCACCAUUUGAAAUCAG UGUUUUAGGAG	103
miR-102-71 (miR-102-7.2)	CUUCAGGAAGCUGGUUUCAUAUGGUGGUUUAGAUU UAAAUAGUGAUUGUCUAGCACCAUUUGAAAUCAGU GUUCUUGGGGG	104
miR-103-2	UUGUGCUUUCAGCUUCUUUACAGUGCUGCCUUGUA GCAUUCAGGUCAAGCAACAUUGUACAGGGCUAUGA AAGAACCA	105
miR-103-1	UACUGCCCUCGGCUUCUUUACAGUGCUGCCUUGUU GCAUAUGGAUCAAGCAGCAUUGUACAGGGCUAUGA AGGCAUUG	106
miR-104-17	AAAUGUCAGACAGCCCAUCGACUGGUGUUGCCAUG AGAUUCAACAGUCAACAUCAGUCUGAUAAGCUACC CGACAAGG	107

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Precursor Name	Sequence (5' To 3')*	SEQ ID NO.
miR-105-1	UGUGCAUCGUGGUCAAAUGCUCAGACUCCUGUGGU GGCUGCUCAUGCACCACGGAUGUUUGAGCAUGUGC UACGGUGUCUA	108
miR-105-2	UGUGCAUCGUGGUCAAAUGCUCAGACUCCUGUGGU GGCUGCUUAUGCACCACGGAUGUUUGAGCAUGUGC UAUGGUGUCUA	109
miR-106-a	CCUUGGCCAUGUAAAAGUGCUUACAGUGCAGGUAG CUUUUUGAGAUCUACUGCAAUGUAAGCACUUCUUA CAUUACCAUGG	110
miR-106-b	CCUGCCGGGGCUAAAGUGCUGACAGUGCAGAUAGU GGUCCUCUCCGUGCUACCGCACUGUGGGUACUUGCU GCUCCAGCAGG	111
miR-107	CUCUCUGCUUUCAGCUUCUUUACAGUGUUGCCUUG UGGCAUGGAGUUCAAGCAGCAUUGUACAGGGCUAU CAAAGCACAGA	112
MIR-108-1-SMALL	ACACUGCAAGAACAAUAAGGAUUUUUAGGGGCAUU AUGACUGAGUCAGAAAACACAGCUGCCCCUGAAAG UCCCUCAUUUUUCUUGCUGU	113
MIR-108-2-SMALL	ACUGCAAGAGCAAUAAGGAUUUUUAGGGGCAUUAU GAUAGUGGAAUGGAAACACAUCUGCCCCCAAAAGU CCCUCAUUUU	114
miR-122a-1	CCUUAGCAGAGCUGUGGAGUGUGACAAUGGUGUUU GUGUCUAAACUAUCAAACGCCAUUAUCACACUAAA UAGCUACUGCUAGGC	115
miR-122a-2	AGCUGUGGAGUGUGACAAUGGUGUUUGUGUCCAAA CUAUCAAACGCCAUUAUCACACUAAAUAGCU	116
miR-123	ACAUUAUUACUUUUGGUACGCGCUGUGACACUUCA AACUCGUACCGUGAGUAAUAAUGCGC	117
miR-124a-1	AGGCCUCUCUCUCCGUGUUCACAGCGGACCUUGAUU UAAAUGUCCAUACAAUUAAGGCACGCGGUGAAUGC CAAGAAUGGGGCUG	118
miR-124a-2	AUCAAGAUUAGAGGCUCUGCUCUCCGUGUUCACAG CGGACCUUGAUUUAAUGUCAUACAAUUAAGGCACG CGGUGAAUGCCAAGAGCGGAGCCUACGGCUGCACU UGAAG	119
miR-124a-3	UGAGGGCCCCUCUGCGUGUUCACAGCGGACCUUGA UUUAAUGUCUAUACAAUUAAGGCACGCGGUGAAUG CCAAGAGAGGCGCCUCC	120
miR-124a	CUCUGCGUGUUCACAGCGGACCUUGAUUUAAUGUC UAUACAAUUAAGGCACGCGGUGAAUGCCAAGAG	121
miR-124b	CUCUCCGUGUUCACAGCGGACCUUGAUUUAAUGUC AUACAAUUAAGGCACGCGGUGAAUGCCAAGAG	122

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Precursor Name	Sequence (5' To 3')*	SEQ ID NO.
miR-125a-1	UGCCAGUCUCUAGGUCCCUGAGACCCUUUAACCUGUGAGGACAUCCAGGGUCACAGGUGAGGUUCUUGGGAGCCUGGCGUCUGGCC	123
miR-125a-2	GGUCCCUGAGACCCUUUAACCUGUGAGGACAUCCAGGGUCACAGGUGAGGUUCUUGGGAGCCUGG	124
miR-125b-1	UGCGCUCCUCUCAGUCCCUGAGACCCUAACUUGUGAUGUUUACCGUUUAAAUCCACGGGUUAGGCUCUUGGGAGCUGCGAGUCGUGCU	125
miR-125b-2	ACCAGACUUUUCCUAGUCCCUGAGACCCUAACUUGUGAGGUAUUUUAGUAACAUCACAAGUCAGGCUCUUGGGACCUAGGCGGAGGGGA	126
miR-126-1	CGCUGGCGACGGGACAUUAUUACUUUUGGUACGCGCUGUGACACUUCAAACUCGUACCGUGAGUAAUAAUGCGCCGUCCACGGCA	127
miR-126-2	ACAUUAUUACUUUUGGUACGCGCUGUGACACUUCAAACUCGUACCGUGAGUAAUAAUGCGC	128
miR-127-1	UGUGAUCACUGUCUCCAGCCUGCUGAAGCUCAGAGGGCUCUGAUUCAGAAAGAUCAUCGGAUCCGUCUGAGCUUGGCUGGUCGGAAGUCUCAUCAUC	129
miR-127-2	CCAGCCUGCUGAAGCUCAGAGGGCUCUGAUUCAGAAAGAUCAUCGGAUCCGUCUGAGCUUGGCUGGUCGG	130
miR-128a	UGAGCUGUUGGAUUCGGGGCCGUAGCACUGUCUGAGAGGUUUACAUUUCUCACAGUGAACCGGUCUCUUUUUCAGCUGCUUC	131
miR-128b	GCCCGGCAGCCACUGUGCAGUGGGAAGGGGGGCCGAUACACUGUACGAGAGUGAGUAGCAGGUCUCACAGUGAACCGGUCUCUUUCCCUACUGUGUCACACUCCUAAUGG	132
miR-128	GUUGGAUUCGGGGCCGUAGCACUGUCUGAGAGGUUUACAUUUCUCACAGUGAACCGGUCUCUUUUUCAGC	133
m*iR-129-1*	UGGAUCUUUUUGCGGUCUGGGCUUGCUGUUCCUCUCAACAGUAGUCAGGAAGCCCUUACCCCAAAAAGUAUCUA	134
MIR-129-2	UGCCCUUCGCGAAUCUUUUUGCGGUCUGGGCUUGCUGUACAUAACUCAAUAGCCGGAAGCCCUUACCCCAAAAAGCAUUUGCGGAGGGCG	135
miR-130a	UGCUGCUGGCCAGAGCUCUUUUCACAUUGUGCUACUGUCUGCACCUGUCACUAGCAGUGCAAUGUUAAAAGGGCAUUGGCCGUGUAGUG	136
miR-131-1	GCCAGGAGGCGGGGUUGGUUGUUAUCUUUGGUUAUCUAGCUGUAUGAGUGGUGUGGAGUCUUCAUAAAGCUAGAUAACCGAAAGUAAAAAUAACCCCAUACACUGCGCAG	137

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Precursor Name	Sequence (5' To 3')*	SEQ ID NO.
miR-131-3	CACGGCGCGGCAGCGGCACUGGCUAAGGGAGGCCCG UUUCUCUCUUUGGUUAUCUAGCUGUAUGAGUGCCA CAGAGCCGUCAUAAAGCUAGAUAACCGAAAGUAGA AAUG	138
miR-131	GUUGUUAUCUUUGGUUAUCUAGCUGUAUGAGUGUA UUGGUCUUCAUAAAGCUAGAUAACCGAAAGUAAAA AC	139
miR-132-1	CCGCCCCCGCGUCUCCAGGGCAACCGUGGCUUUCGA UUGUUACUGUGGGAACUGGAGGUAACAGUCUACAG CCAUGGUCGCCCCGCAGCACGCCCACGCGC	140
miR-132-2	GGGCAACCGUGGCUUUCGAUUGUUACUGUGGGAAC UGGAGGUAACAGUCUACAGCCAUGGUCGCCC	141
miR-133a-1	ACAAUGCUUUGCUAGAGCUGGUAAAAUGGAACCAA AUCGCCUCUUCAAUGGAUUUGGUCCCCUUCAACCAG CUGUAGCUAUGCAUUGA	142
miR-133a-2	GGGAGCCAAAUGCUUUGCUAGAGCUGGUAAAAUGG AACCAAAUCGACUGUCCAAUGGAUUUGGUCCCCUU CAACCAGCUGUAGCUGUGCAUUGAUGGCGCCG	143
miR-133	GCUAGAGCUGGUAAAAUGGAACCAAAUCGCCUCUU CAAUGGAUUUGGUCCCCUUCAACCAGCUGUAGC	144
miR-133b	CCUCAGAAGAAAGAUGCCCCCUGCUCUGGCUGGUCA AACGGAACCAAGUCCGUCUUCCUGAGAGGUUUGGU CCCCUUCAACCAGCUACAGCAGGGCUGGCAAUGCCC AGUCCUUGGAGA	145
MIR-133B-SMALL	GCCCCCUGCUCUGGCUGGUCAAACGGAACCAAGUCC GUCUUCCUGAGAGGUUUGGUCCCCUUCAACCAGCU ACAGCAGGG	146
miR-134-1	CAGGGUGUGUGACUGGUUGACCAGAGGGGCAUGCA CUGUGUUCACCCUGUGGGCCACCUAGUCACCAACCC UC	147
miR-134-2	AGGGUGUGUGACUGGUUGACCAGAGGGGCAUGCAC UGUGUUCACCCUGUGGGCCACCUAGUCACCAACCCU	148
miR-135a-1	AGGCCUCGCUGUUCUCUAUGGCUUUUUAUUCCUAU GUGAUUCUACUGCUCACUCAUAUAGGGAUUGGAGC CGUGGCGCACGGCGGGGACA	149
miR-135a-2 (miR-135-2)	AGAUAAAUUCACUCUAGUGCUUUAUGGCUUUUUAU UCCUAUGUGAUAGUAAUAAAGUCUCAUGUAGGGAU GGAAGCCAUGAAAUACAUUGUGAAAAAUCA	150
miR-135	CUAUGGCUUUUUAUUCCUAUGUGAUUCUACUGCUC ACUCAUAUAGGGAUUGGAGCCGUGG	151
miR-135b	CACUCUGCUGUGGCCUAUGGCUUUUCAUUCCUAUG UGAUUGCUGUCCCAAACUCAUGUAGGGCUAAAAGC CAUGGGCUACAGUGAGGGGCGAGCUCC	152

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Precursor Name	Sequence (5' To 3')*	SEQ ID NO.
miR-136-1	UGAGCCCUCGGAGGACUCCAUUUGUUUUGAUGAUG GAUUCUUAUGCUCCAUCAUCGUCUCAAAUGAGUCU UCAGAGGGUUCU	153
miR-136-2	GAGGACUCCAUUUGUUUUGAUGAUGGAUUCUUAUG CUCCAUCAUCGUCUCAAAUGAGUCUUC	154
miR-137	CUUCGGUGACGGGUAUUCUUGGGUGGAUAAUACGG AUUACGUUGUUAUUGCUUAAGAAUACGCGUAGUCG AGG	155
miR-138-1	CCCUGGCAUGGUGUGGUGGGGCAGCUGGUGUUGUG AAUCAGGCCGUUGCCAAUCAGAGAACGGCUACUUC ACAACACCAGGGCCACACCACACUACAGG	156
miR-138-2	CGUUGCUGCAGCUGGUGUUGUGAAUCAGGCCGACG AGCAGCGCAUCCUCUUACCCGGCUAUUUCACGACAC CAGGGUUGCAUCA	157
miR-138	CAGCUGGUGUUGUGAAUCAGGCCGACGAGCAGCGC AUCCUCUUACCCGGCUAUUUCACGACACCAGGGUUG	158
miR-139	GUGUAUUCUACAGUGCACGUGUCUCCAGUGUGGCU CGGAGGCUGGAGACGCGGCCCUGUUGGAGUAAC	159
miR-140	UGUGUCUCUCUCUGUGUCCUGCCAGUGGUUUUACC CUAUGGUAGGUUACGUCAUGCUGUUCUACCACAGG GUAGAACCACGGACAGGAUACCGGGGCACC	160
miR-140as	UCCUGCCAGUGGUUUUACCCUAUGGUAGGUUACGU CAUGCUGUUCUACCACAGGGUAGAACCACGGACAG GA	161
miR-140s	CCUGCCAGUGGUUUUACCCUAUGGUAGGUUACGUC AUGCUGUUCUACCACAGGGUAGAACCACGGACAGG	162
miR-141-1	CGGCCGGCCCUGGGUCCAUCUUCCAGUACAGUGUUG GAUGGUCUAAUUGUGAAGCUCCUAACACUGUCUGG UAAAGAUGGCUCCCGGGUGGGUUC	163
miR-141-2	GGGUCCAUCUUCCAGUACAGUGUUGGAUGGUCUAA UUGUGAAGCUCCUAACACUGUCUGGUAAAGAUGGC CC	164
miR-142	ACCCAUAAAGUAGAAAGCACUACUAACAGCACUGG AGGGUGUAGUGUUUCCUACUUUAUGGAUG	165
miR-143-1	GCGCAGCGCCCUGUCUCCCAGCCUGAGGUGCAGUGC UGCAUCUCUGGUCAGUUGGGAGUCUGAGAUGAAGC ACUGUAGCUCAGGAAGAGAGAAGUUGUUCUGCAGC	166
miR-143-2	CCUGAGGUGCAGUGCUGCAUCUCUGGUCAGUUGGG AGUCUGAGAUGAAGCACUGUAGCUCAGG	167
miR-144-1	UGGGGCCCUGGCUGGGAUAUCAUCAUAUACUGUAA GUUUGCGAUGAGACACUACAGUAUAGAUGAUGUAC UAGUCCGGGCACCCCC	168

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Precursor Name	Sequence (5' To 3')*	SEQ ID NO.
miR-144-2	GGCUGGGAUAUCAUCAUAUACUGUAAGUUUGCGAU GAGACACUACAGUAUAGAUGAUGUACUAGUC	169
miR-145-1	CACCUUGUCCUCACGGUCCAGUUUUCCCAGGAAUCC CUUAGAUGCUAAGAUGGGGAUUCCUGGAAAUACUG UUCUUGAGGUCAUGGUU	170
miR-145-2	CUCACGGUCCAGUUUUCCCAGGAAUCCCUUAGAUGC UAAGAUGGGGAUUCCUGGAAAUACUGUUCUUGAG	171
miR-146-1	CCGAUGUGUAUCCUCAGCUUUGAGAACUGAAUUCC AUGGGUUGUGUCAGUGUCAGACCUCUGAAAUUCAG UUCUUCAGCUGGGAUAUCUCUGUCAUCGU	172
miR-146-2	AGCUUUGAGAACUGAAUUCCAUGGGUUGUGUCAGU GUCAGACCUGUGAAAUUCAGUUCUUCAGCU	173
miR-147	AAUCUAAAGACAACAUUUCUGCACACACACCAGAC UAUGGAAGCCAGUGUGUGGAAAUGCUUCUGCUAGA UU	174
miR-148a (miR-148)	GAGGCAAAGUUCUGAGACACUCCGACUCUGAGUAU GAUAGAAGUCAGUGCACUACAGAACUUUGUCUC	175
miR-148b	CAAGCACGAUUAGCAUUUGAGGUGAAGUUCUGUUA UACACUCAGGCUGUGGCUCUCUGAAAGUCAGUGCA UCACAGAACUUUGUCUCGAAAGCUUUCUA	176
MIR-148B-SMALL	AAGCACGAUUAGCAUUUGAGGUGAAGUUCUGUUAU ACACUCAGGCUGUGGCUCUCUGAAAGUCAGUGCAU	177
miR-149-1	GCCGGCGCCCGAGCUCUGGCUCCGUGUCUUCACUCC CGUGCUUGUCCGAGGAGGGAGGGAGGGACGGGGGC UGUGCUGGGGCAGCUGGA	178
miR-149-2	GCUCUGGCUCCGUGUCUUCACUCCCGUGCUUGUCCG AGGAGGGAGGGAGGGAC	179
miR-150-1	CUCCCCAUGGCCCUGUCUCCCAACCCUUGUACCAGU GCUGGGCUCAGACCCUGGUACAGGCCUGGGGGACA GGGACCUGGGGAC	180
miR-150-2	CCCUGUCUCCCAACCCUUGUACCAGUGCUGGGCUCA GACCCUGGUACAGGCCUGGGGGACAGGG	181
miR-151	UUUCCUGCCCUCGAGGAGCUCACAGUCUAGUAUGU CUCAUCCCCUACUAGACUGAAGCUCCUUGAGGACAG G	182
MIR-151-2	CCUGUCCUCAAGGAGCUUCAGUCUAGUAGGGGAUG AGACAUACUAGACUGUGAGCUCCUCGAGGGCAGG	183
miR-152-1	UGUCCCCCCCCGGCCCAGGUUCUGUGAUACACUCCGA CUCGGGCUCUGGAGCAGUCAGUGCAUGACAGAACU UGGGCCCGGAAGGACC	184

(continued)

Precursor Name	Sequence (5' To 3')*	SEQ ID NO.
miR-152-2	GGCCCAGGUUCUGUGAUACACUCCGACUCGGGCUCU GGAGCAGUCAGUGCAUGACAGAACUUGGGCCCCGG	185
miR-153-1-1	CUCACAGCUGCCAGUGUCAUUUUUGUGAUCUGCAG CUAGUAUUCUCACUCCAGUUGCAUAGUCACAAAAG UGAUCAUUGGCAGGUGUGGC	186
miR-153-1-2	UCUCUCUCUCCCUCACAGCUGCCAGUGUCAUUGUCA CAAAAGUGAUCAUUGGCAGGUGUGGCUGCUGCAUG	187
miR-153-2-1	AGCGGUGGCCAGUGUCAUUUUUGUGAUGUUGCAGC UAGUAAUAUGAGCCCAGUUGCAUAGUCACAAAAGU GAUCAUUGGAAACUGUG	188
miR-153-2-2	CAGUGUCAUUUUUGUGAUGUUGCAGCUAGUAAUAU GAGCCCAGUUGCAUAGUCACAAAAGUGAUCAUUG	189
miR-154-1	GUGGUACUUGAAGAUAGGUUAUCCGUGUUGCCUUC GCUUUAUUUGUGACGAAUCAUACACGGUUGACCUA UUUUUCAGUACCAA	190
miR-154-2	GAAGAUAGGUUAUCCGUGUUGCCUUCGCUUUAUUU GUGACGAAUCAUACACGGUUGACCUAUUUUUU	191
miR-155	CUGUUAAUGCUAAUCGUGAUAGGGGUUUUUGCCUC CAACUGACUCCUACAUAUUAGCAUUAACAG	192
MIR-156 = MIR-157=OVERL AP MIR-141	CCUAACACUGUCUGGUAAAGAUGGCUCCCGGGUGG GUUCUCUCGGCAGUAACCUUCAGGGAGCCCUGAAG ACCAUGGAGGAC	193
MIR-158-SMALL = MIR-192	GCCGAGACCGAGUGCACAGGGCUCUGACCUAUGAA UUGACAGCCAGUGCUCUCGUCUCCCCUCUGGCUGCC AAUUCCAUAGGUCACAGGUAUGUUCGCCUCAAUGC CAGC	194
MIR-159-1-SMALL	UCCCGCCCCCUGUAACAGCAACUCCAUGUGGAAGUG CCCACUGGUUCCAGUGGGGCUGCUGUUAUCUGGGG CGAGGGCCA	195
MIR-161-SMALL	AAAGCUGGGUUGAGAGGGCGAAAAAGGAUGAGGUG ACUGGUCUGGGCUACGCUAUGCUGCGGCGCUCGGG	196
MIR-163-1B-SMALL	CAUUGGCCUCCUAAGCCAGGGAUUGUGGGUUCGAG UCCCACCCGGGGUAAAGAAAGGCCGAAUU	197
MIR-163-3-SMALL	CCUAAGCCAGGGAUUGUGGGUUCGAGUCCCACCUG GGGUAGAGGUGAAAGUUCCUUUUACGGAAUUUUUU	198
miR-162	CAAUGUCAGCAGUGCCUUAGCAGCACGUAAAUAUU GGCGUUAAGAUUCUAAAAUUAUCUCCAGUAUUAAC UGUGCUGCUGAAGUAAGGUUGACCAUACUCUACAG UUG	199
MIR-175-SMALL=MIR-224	GGGCUUUCAAGUCACUAGUGGUUCCGUUUAGUAGA UGAUUGUGCAUUGUUUCAAAAUGGUGCCCUAGUGA CUACAAAGCCC	200

(continued)

Precursor Name	Sequence (5' To 3')*	SEQ ID NO.
MIR-177-SMALL	ACGCAAGUGUCCUAAGGUGAGCUCAGGGAGCACAG AAACCUCCAGUGGAACAGAAGGGCAAAAGCUCAUU	201
MIR-180-SMALL	CAUGUGUCACUUUCAGGUGGAGUUUCAAGAGUCCC UUCCUGGUUCACCGUCUCCUUUGCUCUUCCACAAC	202
miR-181a	AGAAGGGCUAUCAGGCCAGCCUUCAGAGGACUCCA AGGAACAUUCAACGCUGUCGGUGAGUUUGGGAUUU GAAAAAACCACUGACCGUUGACUGUACCUUGGGGU CCUUA	203
miR-181b-1	CCUGUGCAGAGAUUAUUUUUUAAAAGGUCACAAUC AACAUUCAUUGCUGUCGGUGGGUUGAACUGUGUGG ACAAGCUCACUGAACAAUGAAUGCAACUGUGGCCC CGCUU	204
miR-181b-2	CUGAUGGCUGCACUCAACAUUCAUUGCUGUCGGUG GGUUUGAGUCUGAAUCAACUCACUGAUCAAUGAAU GCAAACUGCGGACCAAACA	205
mIR-181c	CGGAAAAUUUGCCAAGGGUUUGGGGGAACAUUCAA CCUGUCGGUGAGUUUGGGCAGCUCAGGCAAACCAU CGACCGUUGAGUGGACCCUGAGGCCUGGAAUUGCC AUCCU	206
miR-182-as	GAGCUGCUUGCCUCCCCCCGUUUUUGGCAAUGGUA GAACUCACACUGGUGAGGUAACAGGAUCCGGUGGU UCUAGACUUGCCAACUAUGGGGCGAGGACUCAGCC GGCAC	207
miR-182	UUUUUGGCAAUGGUAGAACUCACACUGGUGAGGUA ACAGGAUCCGGUGGUUCUAGACUUGCCAACUAUGG	208
miR-183	CCGCAGAGUGUGACUCCUGUUCUGUGUAUGGCACU GGUAGAAUUCACUGUGAACAGUCUCAGUCAGUGAA UUACCGAAGGGCCAUAAACAGAGCAGAGACAGAUC CACGA	209
miR-184-1	CCAGUCACGUCCCCUUAUCACUUUUCCAGCCCAGCU UUGUGACUGUAAGUGUUGGACGGAGAACUGAUAAG GGUAGGUGAUUGA	210
miR-184-2	CCUUAUCACUUUUCCAGCCCAGCUUUGUGACUGUA AGUGUUGGACGGAGAACUGAUAAGGGUAGG	211
miR-185-1	AGGGGGCGAGGGAUUGGAGAGAAAGGCAGUUCCUG AUGGUCCCCUCCCCAGGGGCUGGCUUUCCUCUGGUC CUUCCCUCCCA	212
miR-185-2	AGGGAUUGGAGAGAAAGGCAGUUCCUGAUGGUCCC CUCCCCAGGGGCUGGCUUUCCUCUGGUCCUU	213
miR-186-1	UGCUUGUAACUUUCCAAAGAAUUCUCCUUUUGGGC UUUCUGGUUUUAUUUUAAGCCCAAAGGUGAAUUUU UUGGGAAGUUUGAGCU	214

(continued)

Precursor Name	Sequence (5' To 3')*	SEQ ID NO.
miR-186-2	ACUUUCCAAAGAAUUCUCCUUUUGGGCUUUCUGGU UUUAUUUUAAGCCCAAAGGUGAAUUUUUUGGGAAG U	215
miR-187	GGUCGGGCUCACCAUGACACAGUGUGAGACUCGGG CUACAACACAGGACCCGGGGCGCUGCUCUGACCCCU CGUGUCUUGUGUUGCAGCCGGAGGGACGCAGGUCC GCA	216
miR-188-1	UGCUCCCUCUCUCACAUCCCUUGCAUGGUGGAGGGU GAGCUUUCUGAAAACCCCUCCCACAUGCAGGGUUU GCAGGAUGGCGAGCC	217
miR-188-2	UCUCACAUCCCUUGCAUGGUGGAGGGUGAGCUUUC UGAAAACCCCUCCCACAUGCAGGGUUUGCAGGA	218
miR-189-1	CUGUCGAUUGGACCCGCCCUCCGGUGCCUACUGAGC UGAUAUCAGUUCUCAUUUUACACACUGGCUCAGUU CAGCAGGAACAGGAGUCGAGCCCUUGAGCAA	219
miR-189-2	CUCCGGUGCCUACUGAGCUGAUAUCAGUUCUCAUU UUACACACUGGCUCAGUUCAGCAGGAACAGGAG	220
miR-190-1	UGCAGGCCUCUGUGUGAUAUGUUUGAUAUAUUAGG UUGUUAUUUAAUCCAACUAUAUAUCAAACAUAUUC CUACAGUGUCUUGCC	221
miR-190-2	CUGUGUGAUAUGUUUGAUAUAUUAGGUUGUUAUUU AAUCCAACUAUAUAUCAAACAUAUUCCUACAG	222
miR-191-1	CGGCUGGACAGCGGGCAACGGAAUCCCAAAAGCAG CUGUUGUCUCCAGAGCAUUCCAGCUGCGCUUGGAU UUCGUCCCCUGCUCUCCUGCCU	223
miR-191-2	AGCGGGCAACGGAAUCCCAAAAGCAGCUGUUGUCU CCAGAGCAUUCCAGCUGCGCUUGGAUUUCGUCCCCU GCU	224
miR-192-2/3	CCGAGACCGAGUGCACAGGGCUCUGACCUAUGAAU UGACAGCCAGUGCUCUCGUCUCCCCUCUGGCUGCCA AUUCCAUAGGUCACAGGUAUGUUCGCCUCAAUGCC AG	225
miR-192	GCCGAGACCGAGUGCACAGGGCUCUGACCUAUGAA UUGACAGCCAGUGCUCUCGUCUCCCCUCUGGCUGCC AAUUCCAUAGGUCACAGGUAUGUUCGCCUCAAUGC CAGC	226
miR-193-1	CGAGGAUGGGAGCUGAGGGCUGGGUCUUUGCGGGC GAGAUGAGGGUGUCGGAUCAACUGGCCUACAAAGU CCCAGUUCUCGGCCCCCG	227
miR-193-2	GCUGGGUCUUUGCGGGCGAGAUGAGGGUGUCGGAU CAACUGGCCUACAAAGUCCCAGU	228
miR-194-1	AUGGUGUUAUCAAGUGUAACAGCAACUCCAUGUGG ACUGUGUACCAAUUUCCAGUGGAGAUGCUGUUACU UUUGAUGGUUACCAA	229

(continued)

Precursor Name	Sequence (5' To 3')*	SEQ ID NO.
miR-194-2	GUGUAACAGCAACUCCAUGUGGACUGUGUACCAAU UUCCAGUGGAGAUGCUGUUACUUUUGAU	230
miR-195-1	AGCUUCCCUGGCUCUAGCAGCACAGAAAUAUUGGC ACAGGGAAGCGAGUCUGCCAAUAUUGGCUGUGCUG CUCCAGGCAGGGUGGUG	231
miR-195-2	UAGCAGCACAGAAAUAUUGGCACAGGGAAGCGAGU CUGCCAAUAUUGGCUGUGCUGCU	232
miR-196-1	CUAGAGCUUGAAUUGGAACUGCUGAGUGAAUUAGG UAGUUUCAUGUUGUUGGGCCUGGGUUUCUGAACAC AACAACAUUAAACCACCCGAUUCACGGCAGUUACU GCUCC	233
miR-196a-1	GUGAAUUAGGUAGUUUCAUGUUGUUGGGCCUGGGU UUCUGAACACAACAACAUUAAACCACCCGAUUCAC	234
miR-196a-2 (miR-196-2)	UGCUCGCUCAGCUGAUCUGUGGCUUAGGUAGUUUC AUGUUGUUGGGAUUGAGUUUUGAACUCGGCAACAA GAAACUGCCUGAGUUACAUCAGUCGGUUUUCGUCG AGGGC	235
miR-196	GUGAAUUAGGUAGUUUCAUGUUGUUGGGCCUGGGU UUCUGAACACAACAACAUUAAACCACCCGAUUCAC	236
miR-196b	ACUGGUCGGUGAUUUAGGUAGUUUCCUGUUGUUGG GAUCCACCUUUCUCUCGACAGCACGACACUGCCUUC AUUACUUCAGUUG	237
miR-197	GGCUGUGCCGGGUAGAGAGGGCAGUGGGAGGUAAG AGCUCUUCACCCUUCACCACCUUCUCCACCCAGCAU GGCC	238
MIR-197-2	GUGCAUGUGUAUGUAUGUGUGCAUGUGCAUGUGUA UGUGUAUGAGUGCAUGCGUGUGUGC	239
miR-198	UCAUUGGUCCAGAGGGGAGAUAGGUUCCUGUGAUU UUUCCUUCUUCUCUAUAGAAUAAAUGA	240
miR-199a-1	GCCAACCCAGUGUUCAGACUACCUGUUCAGGAGGC UCUCAAUGUGUACAGUAGUCUGCACAUUGGUUAGG C	241
miR-199a-2	AGGAAGCUUCUGGAGAUCCUGCUCCGUCGCCCCAGU GUUCAGACUACCUGUUCAGGACAAUGCCGUUGUAC AGUAGUCUGCACAUUGGUUAGACUGGGCAAGGGAG AGCA	242
miR-199b	CCAGAGGACACCUCCACUCCGUCUACCCAGUGUUUA GACUAUCUGUUCAGGACUCCCAAAUUGUACAGUAG UCUGCACAUUGGUUAGGCUGGGCUGGGUUAGACCC UCGG	243
miR-199s	GCCAACCCAGUGUUCAGACUACCUGUUCAGGAGGC UCUCAAUGUGUACAGUAGUCUGCACAUUGGUUAGG C	244

(continued)

Precursor Name	Sequence (5' To 3')*	SEQ ID NO.
miR-200a	GCCGUGGCCAUCUUACUGGGCAGCAUUGGAUGGAG UCAGGUCUCUAAUACUGCCUGGUAAUGAUGACGGC	245
miR-200b	CCAGCUCGGGCAGCCGUGGCCAUCUUACUGGGCAGC AUUGGAUGGAGUCAGGUCUCUAAUACUGCCUGGUA AUGAUGACGGCGGAGCCCUGCACG	246
m*iR-200c*	CCCUCGUCUUACCCAGCAGUGUUUGGGUGCGGUUG GGAGUCUCUAAUACUGCCGGGUAAUGAUGGAGG	247
miR-202	GUUCCUUUUUCCUAUGCAUAUACUUCUUUGAGGAU CUGGCCUAAAGAGGUAUAGGGCAUGGGAAGAUGGA GC	248
miR-203	GUGUUGGGGACUCGCGCGCUGGGUCCAGUGGUUCU UAACAGUUCAACAGUUCUGUAGCGCAAUUGUGAAA UGUUUAGGACCACUAGACCCGGCGGGCGCGGCGAC AGCGA	249
miR-204	GGCUACAGUCUUUCUUCAUGUGACUCGUGGACUUC CCUUUGUCAUCCUAUGCCUGAGAAUAUAUGAAGGA GGCUGGGAAGGCAAAGGGACGUUCAAUUGUCAUCA CUGGC	250
miR-205	AAAGAUCCUCAGACAAUCCAUGUGCUUCUCUUGUC CUUCAUUCCACCGGAGUCUGUCUCAUACCCAACCAG AUUUCAGUGGAGUGAAGUUCAGGAGGCAUGGAGCU GACA	251
miR-206-1	UGCUUCCCGAGGCCACAUGCUUCUUUAUAUCCCCAU AUGGAUUACUUUGCUAUGGAAUGUAAGGAAGUGUG UGGUUUCGGCAAGUG	252
miR-206-2	AGGCCACAUGCUUCUUUAUAUCCCCAUAUGGAUUA CUUUGCUAUGGAAUGUAAGGAAGUGUGUGGUUUU	253
miR-208	UGACGGGCGAGCUUUUGGCCCGGGUUAUACCUGAU GCUCACGUAUAAGACGAGCAAAAAGCUUGUUGGUC A	254
miR-210	ACCCGGCAGUGCCUCCAGGCGCAGGGCAGCCCCUGC CCACCGCACACUGCGCUGCCCCAGACCCACUGUGCG UGUGACAGCGGCUGAUCUGUGCCUGGGCAGCGCGA CCC	255
miR-211	UCACCUGGCCAUGUGACUUGUGGGCUUCCCUUUGU CAUCCUUCGCCUAGGGCUCUGAGCAGGGCAGGGAC AGCAAAGGGGUGCUCAGUUGUCACUUCCCACAGCA CGGAG	256
miR-212	CGGGGCACCCCGCCCGGACAGCGCGCCGGCACCUUG GCUCUAGACUGCUUACUGCCCGGGCCGCCCUCAGUA ACAGUCUCCAGUCACGGCCACCGACGCCUGGCCCCG CC	257

(continued)

Precursor Name	Sequence (5' To 3')*	SEQ ID NO.
miR-213-2	CCUGUGCAGAGAUUAUUUUUUAAAAGGUCACAAUC AACAUUCAUUGCUGUCGGUGGGUUGAACUGUGUGG ACAAGCUCACUGAACAAUGAAUGCAACUGUGGCCC CGCUU	258
miR-213	GAGUUUUGAGGUUGCUUCAGUGAACAUUCAACGCU GUCGGUGAGUUUGGAAUUAAAAUCAAAACCAUCGA CCGUUGAUUGUACCCUAUGGCUAACCAUCAUCUAC UCC	259
miR-214	GGCCUGGCUGGACAGAGUUGUCAUGUGUCUGCCUG UCUACACUUGCUGUGCAGAACAUCCGCUCACCUGUA CAGCAGGCACAGACAGGCAGUCACAUGACAACCCAG CCU	260
miR-215	AUCAUUCAGAAAUGGUAUACAGGAAAAUGACCUAU GAAUUGACAGACAAUAUAGCUGAGUUUGUCUGUCA UUUCUUUAGGCCAAUAUUCUGUAUGACUGUGCUAC UUCAA	261
miR-216	GAUGGCUGUGAGUUGGCUUAAUCUCAGCUGGCAAC UGUGAGAUGUUCAUACAAUCCCUCACAGUGGUCUC UGGGAUUAUGCUAAACAGAGCAAUUUCCUAGCCCU CACGA	262
miR-217	AGUAUAAUUAUUACAUAGUUUUUGAUGUCGCAGAU ACUGCAUCAGGAACUGAUUGGAUAAGAAUCAGUCA CCAUCAGUUCCUAAUGCAUUGCCUUCAGCAUCUAA ACAAG	263
miR-218-1	GUGAUAAUGUAGCGAGAUUUUCUGUUGUGCUUGAU CUAACCAUGUGGUUGCGAGGUAUGAGUAAAACAUG GUUCCGUCAAGCACCAUGGAACGUCACGCAGCUUUC UACA	264
miR-218-2	GACCAGUCGCUGCGGGGCUUUCCUUUGUGCUUGAU CUAACCAUGUGGUGGAACGAUGGAAACGGAACAUG GUUCUGUCAAGCACCGCGGAAAGCACCGUGCUCUCC UGCA	265
miR-219	CCGCCCCGGGCCGCGGCUCCUGAUUGUCCAAACGCA AUUCUCGAGUCUAUGGCUCCGGCCGAGAGUUGAGU CUGGACGUCCCGAGCCGCCGCCCCCAAACCUCGAGC GGG	266
miR-219-1	CCGCCCCGGGCCGCGGCUCCUGAUUGUCCAAACGCA AUUCUCGAGUCUAUGGCUCCGGCCGAGAGUUGAGU CUGGACGUCCCGAGCCGCCGCCCCCAAACCUCGAGC GGG	267
miR-219-2	ACUCAGGGGCUUCGCCACUGAUUGUCCAAACGCAA UUCUUGUACGAGUCUGCGGCCAACCGAGAAUUGUG GCUGGACAUCUGUGGCUGAGCUCCGGG	268
miR-220	GACAGUGUGGCAUUGUAGGGCUCCACACCGUAUCU GACACUUUGGGCGAGGGCACCAUGCUGAAGGUGUU CAUGAUGCGGUCUGGGAACUCCUCACGGAUCUUAC UGAUG	269

(continued)

Precursor Name	Sequence (5' To 3')*	SEQ ID NO.
miR-221	UGAACAUCCAGGUCUGGGGCAUGAACCUGGCAUAC AAUGUAGAUUUCUGUGUUCGUUAGGCAACAGCUAC AUUGUCUGCUGGGUUUCAGGCUACCUGGAAACAUG UUCUC	270
miR-222	GCUGCUGGAAGGUGUAGGUACCCUCAAUGGCUCAG UAGCCAGUGUAGAUCCUGUCUUUCGUAAUCAGCAG CUACAUCUGGCUACUGGGUCUCUGAUGGCAUCUUC UAGCU	271
miR-223	CCUGGCCUCCUGCAGUGCCACGCUCCGUGUAUUUGA CAAGCUGAGUUGGACACUCCAUGUGGUAGAGUGUC AGUUUGUCAAAUACCCCAAGUGCGGCACAUGCUUA CCAG	272
miR-224	GGGCUUUCAAGUCACUAGUGGUUCCGUUUAGUAGA UGAUUGUGCAUUGUUUCAAAAUGGUGCCCUAGUGA CUACAAAGCCC	273
MIR-294-1 (CHR16)	CAAUCUUCCUUUAUCAUGGUAUUGAUUUUUCAGUG CUUCCCUUUUGUGUGAGAGAAGAUA	274
miR-296	AGGACCCUUCCAGAGGGCCCCCCCUCAAUCCUGUUG UGCCUAAUUCAGAGGGUUGGGUGGAGGCUCUCCUG AAGGGCUCU	275
miR-299	AAGAAAUGGUUUACCGUCCCACAUACAUUUUGAAU AUGUAUGUGGGAUGGUAAACCGCUUCUU	276
miR-301	ACUGCUAACGAAUGCUCUGACUUUAUUGCACUACU GUACUUUACAGCUAGCAGUGCAAUAGUAUUGUCAA AGCAUCUGAAAGCAGG	277
miR-302a	CCACCACUUAAACGUGGAUGUACUUGCUUUGAAAC UAAAGAAGUAAGUGCUUCCAUGUUUUGGUGAUGG	278
miR-302b	GCUCCCUUCAACUUUAACAUGGAAGUGCUUUCUGU GACUUUAAAAGUAAGUGCUUCCAUGUUUUAGUAGG AGU	279
miR-302c	CCUUUGCUUUAACAUGGGGGUACCUGCUGUGUGAA ACAAAAGUAAGUGCUUCCAUGUUUCAGUGGAGG	280
miR-302d	CCUCUACUUUAACAUGGAGGCACUUGCUGUGACAU GACAAAAAUAAGUGCUUCCAUGUUUGAGUGUGG	281
miR-320	GCUUCGCUCCCCUCCGCCUUCUCUUCCCGGUUCUUC CCGGAGUCGGGAAAAGCUGGGUUGAGAGGGCGAAA AAGGAUGAGGU	282
miR-321	UUGGCCUCCUAAGCCAGGGAUUGUGGGUUCGAGUC CCACCCGGGGUAAAGAAAGGCCGA	283
miR-323	UUGGUACUUGGAGAGAGGUGGUCCGUGGCGCGUUC GCUUUAUUUAUGGCGCACAUUACACGGUCGACCUC UUUGCAGUAUCUAAUC	284

(continued)

Precursor Name	Sequence (5' To 3')*	SEQ ID NO.
miR-324	CUGACUAUGCCUCCCCGCAUCCCCUAGGGCAUUGGU GUAAAGCUGGAGACCCACUGCCCCAGGUGCUGCUG GGGGUUGUAGUC	285
miR-325	AUACAGUGCUUGGUUCCUAGUAGGUGUCCAGUAAG UGUUUGUGACAUAAUUUGUUUAUUGAGGACCUCCU AUCAAUCAAGCACUGUGCUAGGCUCUGG	286
miR-326	CUCAUCUGUCUGUUGGGCUGGAGGCAGGGCCUUUG UGAAGGCGGGUGGUGCUCAGAUCGCCUCUGGGCCC UUCCUCCAGCCCCGAGGCGGAUUCA	287
miR-328	UGGAGUGGGGGGGCAGGAGGGGCUCAGGGAGAAAG UGCAUACAGCCCCUGGCCCUCUCUGCCCUUCCGUCC CCUG	288
miR-330	CUUUGGCGAUCACUGCCUCUCUGGGCCUGUGUCUU AGGCUCUGCAAGAUCAACCGAGCAAAGCACACGGCC UGCAGAGAGGCAGCGCUCUGCCC	289
miR-331	GAGUUUGGUUUUGUUUGGGUUUGUUCUAGGUAUGG UCCCAGGGAUCCCAGAUCAAACCAGGCCCCUGGGCC UAUCCUAGAACCAACCUAAGCUC	290
miR-335	UGUUUUGAGCGGGGGUCAAGAGCAAUAACGAAAAA UGUUUGUCAUAAACCGUUUUUCAUUAUUGCUCCUG ACCUCCUCUCAUUUGCUAUAUUCA	291
miR-337	GUAGUCAGUAGUUGGGGGGUGGGAACGGCUUCAUA CAGGAGUUGAUGCACAGUUAUCCAGCUCCUAUAUG AUGCCUUUCUUCAUCCCCUUCAA	292
miR-338	UCUCCAACAAUAUCCUGGUGCUGAGUGAUGACUCA GGCGACUCCAGCAUCAGUGAUUUUGUUGAAGA	293
miR-339	CGGGGCGGCCGCUCUCCCUGUCCUCCAGGAGCUCAC GUGUGCCUGCCUGUGAGCGCCUCGACGACAGAGCCG GCGCCUGCCCCAGUGUCUGCGC	294
miR-340	UUGUACCUGGUGUGAUUAUAAAGCAAUGAGACUGA UUGUCAUAUGUCGUUUGUGGGAUCCGUCUCAGUUA CUUUAUAGCCAUACCUGGUAUCUUA	295
miR-342	GAAACUGGGCUCAAGGUGAGGGGUGCUAUCUGUGA UUGAGGGACAUGGUUAAUGGAAUUGUCUCACACAG AAAUCGCACCCGUCACCUUGGCCUACUUA	296
miR-345	ACCCAAACCCUAGGUCUGCUGACUCCUAGUCCAGGG CUCGUGAUGGCUGGUGGGCCCUGAACGAGGGGUCU GGAGGCCUGGGUUUGAAUAUCGACAGC	297
miR-346	GUCUGUCUGCCCGCAUGCCUGCCUCUCUGUUGCUCU GAAGGAGGCAGGGGCUGGGCCUGCAGCUGCCUGGG CAGAGCGGCUCCUGC	298
miR-367	CCAUUACUGUUGCUAAUAUGCAACUCUGUUGAAUA UAAAUUGGAAUUGCACUUUAGCAAUGGUGAUGG	299

(continued)

Precursor Name	Sequence (5' To 3')*	SEQ ID NO.
miR-368	AAAAGGUGGAUAUUCCUUCUAUGUUUAUGUUAUUU AUGGUUAAACAUAGAGGAAAUUCCACGUUUU	300
miR-369	UUGAAGGGAGAUCGACCGUGUUAUAUUCGCUUUAU UGACUUCGAAUAAUACAUGGUUGAUCUUUUCUCAG	301
miR-370	AGACAGAGAAGCCAGGUCACGUCUCUGCAGUUACA CAGCUCACGAGUGCCUGCUGGGGUGGAACCUGGUC UGUCU	302
miR-371	GUGGCACUCAAACUGUGGGGGCACUUUCUGCUCUC UGGUGAAAGUGCCGCCAUCUUUUGAGUGUUAC	303
miR-372	GUGGGCCUCAAAUGUGGAGCACUAUUCUGAUGUCC AAGUGGAAAGUGCUGCGACAUUUGAGCGUCAC	304
miR-373	GGGAUACUCAAAAUGGGGGCGCUUUCCUUUUUGUC UGUACUGGGAAGUGCUUCGAUUUUGGGGUGUCCC	305
miR-374	UACAUCGGCCAUUAUAAUACAACCUGAUAAGUGUU AUAGCACUUAUCAGAUUGUAUUGUAAUUGUCUGUG UA	306
mir-hes1	AUGGAGCUGCUCACCCUGUGGGCCUCAAAUGUGGA GGAACUAUUCUGAUGUCCAAGUGGAAAGUGCUGCG ACAUUUGAGCGUCACCGGUGACGCCCAUAUCA	307
mir-hes2	GCAUCCCCUCAGCCUGUGGCACUCAAACUGUGGGGG CACUUUCUGCUCUCUGGUGAAAGUGCCGCCAUCUU UUGAGUGUUACCGCUUGAGAAGACUCAACC	308
mir-hes3	CGAGGAGCUCAUACUGGGAUACUCAAAAUGGGGGC GCUUUCCUUUUUGUCUGUUACUGGGAAGUGCUUCG AUUUUGGGGUGUCCCUGUUUGAGUAGGGCAUC	309

[0059] * An underlined sequence within a precursor sequence corresponds to a mature processed miR transcript (see Table 1b). Some precursor sequences have two underlined sequences denoting two different mature miRs that are derived from the same precursor. All sequences are human.

[0060]

Table 1b: Human Mature microRNA Sequences.

Mature miRNA Name	Mature miRNA Sequence (5' to 3')	SEQ ID NO.	Corresponding precursor microRNA (s); see Table 1a
let-7a	UGAGGUAGUAGGUUG UAUAGUU	310	*let-7a-1; let-7a-2; let-7a-3; let-7a-4*
let-7b	UGAGGUAGUAGGUUG UGUGGUU	311	*let-7b*
let-7c	UGAGGUAGUAGGUUG UAUGGUU	312	*let-7c*
let-7d	AGAGGUAGUAGGUUG CAUAGU	313	*let-7d; let-7d-v1*

(continued)

Mature miRNA Name	Mature miRNA Sequence (5' to 3')	SEQ ID NO.	Corresponding precursor microRNA (s); see Table 1a
let-7e	UGAGGUAGGAGGUUG UAUAGU	314	*let-7e*
let-7f	UGAGGUAGUAGAUUG UAUAGUU	315	*let-7f-1; let-7f-2-1; let-7f-2-2*
let-7g	UGAGGUAGUAGUUUG UACAGU	316	*let-7g*
let-7i	UGAGGUAGUAGUUUG UGCU	317	*let-7i*
miR-1	UGGAAUGUAAAGAAG UAUGUA	318	*miR-1b; miR-1b-1; miR-1b-2*
miR-7	UGGAAGACUAGUGAU UUUGUU	319	*miR-7-1; miR-7-1a, miR-7-2; miR-7-3*
miR-9	UCUUUGGUUAUCUAGC UGUAUGA	320	*miR-9-1; miR-9-2; miR-9-3*
*miR-9**	UAAAGCUAGAUAACCG AAAGU	321	*miR-9-1; miR-9-2; miR-9-3*
miR-10a	UACCCUGUAGAUCCGA AUUUGUG	322	*miR-10a*
miR-10b	UACCCUGUAGAACCGA AUUUGU	323	*miR-10b*
miR-15a	UAGCAGCACAUAAUGG UUUGUG	324	*miR-15a; miR-15a-2*
miR-15b	UAGCAGCACAUCAUGG UUUACA	325	*miR-15b*
miR-16	UAGCAGCACGUAAAUA UUGGCG	326	*miR-16-1; miR-16-2; miR-16-13*
miR-17-5p	CAAAGUGCUUACAGUG CAGGUAGU	327	*miR-17*
miR-17-3p	ACUGCAGUGAAGGCAC UUGU	328	*miR-17*
miR-18	UAAGGUGCAUCUAGUG CAGAUA	329	*miR-18; miR-18-13*
miR-19a	UGUGCAAAUCUAUGCA AAACUGA	330	*miR-19a; miR-19a-13*
miR-19b	UGUGCAAAUCCAUGCA AAACUGA	331	*miR-19b-1; miR-19b-2*
miR-20	UAAAGUGCUUAUAGU GCAGGUA	332	*miR-20 (miR-20a)*

(continued)

Mature miRNA Name	Mature miRNA Sequence (5' to 3')	SEQ ID NO.	Corresponding precursor microRNA (s); see Table 1a
miR-21	UAGCUUAUCAGACUGA UGUUGA	333	*miR-21; miR-21-17*
miR-22	AAGCUGCCAGUUGAAG AACUGU	334	*miR-22*
miR-23a	AUCACAUUGCCAGGGA UUUCC	335	*miR-23a*
miR-23b	AUCACAUUGCCAGGGA UUACCAC	336	*miR-23b*
miR-24	UGGCUCAGUUCAGCAG GAACAG	337	*miR-24-1; miR-24-2; miR-24-19; miR-24-9*
miR-25	CAUUGCACUUGUCUCG GUCUGA	338	*miR-25*
miR-26a	UUCAAGUAAUCCAGGA UAGGCU	339	*miR-26a; miR-26a-1; miR-26a-2*
miR-26b	UUCAAGUAAUUCAGGA UAGGU	340	*miR-26b*
miR-27a	UUCACAGUGGCUAAGU UCCGCC	341	*miR-27a*
miR-27b	UUCACAGUGGCUAAGU UCUG	342	*miR-27b-1; miR-27b-2*
miR-28	AAGGAGCUCACAGUCU AUUGAG	343	*miR-28*
miR-29a	CUAGCACCAUCUGAAA UCGGUU	344	*miR-29a-2; miR-29a*
miR-29b	UAGCACCAUUUGAAAU CAGU	345	*miR-29b-1; miR-29b-2*
miR-29c	UAGCACCAUUUGAAAU CGGUUA	346	*miR-29c*
miR-30a-5p	UGUAAACAUCCUCGAC UGGAAGC	347	*miR-30a*
miR-30a-3p	CUUUCAGUCGGAUGUU UGCAGC	348	*miR-30a*
miR-30b	UGUAAACAUCCUACAC UCAGC	349	*miR-30b-1; miR-30b-2*
miR-30c	UGUAAACAUCCUACAC UCUCAGC	350	*miR-30c*
miR-30d	UGUAAACAUCCCCGAC UGGAAG	351	*miR-30d*

(continued)

Mature miRNA Name	Mature miRNA Sequence (5' to 3')	SEQ ID NO.	Corresponding precursor microRNA (s); see Table 1a
miR-30e	UGUAAACAUCCUUGACUGGA	352	*miR-30e*
miR-31	GGCAAGAUGCUGGCAUAGCUG	353	*miR-31*
miR-32	UAUUGCACAUUACUAAGUUGC	354	*miR-32*
miR-33	GUGCAUUGUAGUUGCAUUG	355	*miR-33; miR-33b*
miR-34a	UGGCAGUGUCUUAGCUGGUUGU	356	*miR-34a*
miR-34b	AGGCAGUGUCAUUAGCUGAUUG	357	*miR-34b*
miR-34c	AGGCAGUGUAGUUAGCUGAUUG	358	*miR-34c*
miR-92	UAUUGCACUUGUCCCGGCCUGU	359	*miR-92-2; miR-92-1*
miR-93	AAAGUGCUGUUCGUGCAGGUAG	360	*miR-93-1; miR-93-2*
miR-95	UUCAACGGGUAUUUAUUGAGCA	361	*miR-95*
miR-96	UUUGGCACUAGCACAUUUUUGC	362	*miR-96*
miR-98	UGAGGUAGUAAGUUGUAUUGUU	363	*miR-98*
miR-99a	AACCCGUAGAUCCGAUCUUGUG	364	*miR-99a*
miR-99b	CACCCGUAGAACCGACCUUGCG	365	*miR-99b*
miR-100	UACAGUACUGUGAUAACUGAAG	366	*miR-100*
miR-101	UACAGUACUGUGAUAACUGAAG	367	*miR-101-1; miR-101-2*
miR-103	AGCAGCAUUGUACAGGGCUAUGA	368	*miR-103-1*
miR-105	UCAAAUGCUCAGACUCCUGU	369	*miR-105*
miR-106-a	AAAAGUGCUUACAGUGCAGGUAGC	370	*miR-106-a*

(continued)

Mature miRNA Name	Mature miRNA Sequence (5' to 3')	SEQ ID NO.	Corresponding precursor microRNA (s); see Table 1a
miR-106-b	UAAAGUGCUGACAGUG CAGAU	371	*miR-106-b*
miR-107	AGCAGCAUUGUACAGG GCUAUCA	372	*miR-107*
miR-122a	UGGAGUGUGACAAUG GUGUUUGU	373	*miR-122a-1; miR-122a-2*
miR-124a	UUAAGGCACGCGGUGA AUGCCA	374	*miR-124a-1; miR-124a-2; miR-124a-3*
miR-125a	UCCCUGAGACCCUUUA ACCUGUG	375	*miR-125a-1; miR-125a-2*
miR-125b	UCCCUGAGACCCUAAC UUGUGA	376	*miR-125b-1; miR-125b-2*
*miR-126**	CAUUAUUACUUUUGGU ACGCG	377	*miR-126-1; miR-126-2*
miR-126	UCGUACCGUGAGUAAU AAUGC	378	*miR-126-1; miR-126-2*
miR-127	UCGGAUCCGUCUGAGC UUGGCU	379	*miR-127-1; miR-127-2*
miR-128a	UCACAGUGAACCGGUC UCUUUU	380	*miR-128; miR-128a*
miR-128b	UCACAGUGAACCGGUC UCUUUC	381	*miR-128b*
miR-129	CUUUUUGCGGUCUGGG CUUGC	382	*miR-129-1; miR-129-2*
miR-130a	CAGUGCAAUGUUAAAA GGGC	383	*miR-130a*
miR-130b	CAGUGCAAUGAUGAAA GGGCAU	384	*miR-130b*
miR-132	UAACAGUCUACAGCCA UGGUCG	385	*miR-132-1*
miR-133a	UUGGUCCCCUUCAACC AGCUGU	386	*miR-133a-1; miR-133a-2*
miR-133b	UUGGUCCCCUUCAACC AGCUA	387	*miR-133b*
miR-134	UGUGACUGGUUGACCA GAGGG	388	*miR-134-1; miR-134-2*
miR-135a	UAUGGCUUUUUAUUCC UAUGUGA	389	*miR-135a; miR-135a-2 (miR-135-2)*

(continued)

Mature miRNA Name	Mature miRNA Sequence (5' to 3')	SEQ ID NO.	Corresponding precursor microRNA (s); see Table 1a
miR-135b	UAUGGCUUUUCAUUCC UAUGUG	390	*miR-135b*
miR-136	ACUCCAUUUGUUUUGA UGAUGGA	391	*miR-136-1; miR-136-2*
miR-137	UAUUGCUUAAGAAUAC GCGUAG	392	*miR-137*
miR-138	AGCUGGUGUUGUGAA UC	393	*miR-138-1; miR-138-2*
miR-139	UCUACAGUGCACGUGU CU	394	*miR-139*
miR-140	AGUGGUUUUACCCUAU GGUAG	395	*miR-140; miR-140as; miR-140s*
miR-141	AACACUGUCUGGUAAA GAUGG	396	*miR-141-; miR-141-2*
miR-142-3p	UGUAGUGUUUCCUACU UUAUGGA	397	*miR-142*
miR-142-5p	CAUAAAGUAGAAAGCA CUAC	398	*miR-142*
miR-143	UGAGAUGAAGCACUGU AGCUCA	399	*miR-143-1*
miR-144	UACAGUAUAGAUGAU GUACUAG	400	*miR-144-1; miR-144-2*
miR-145	GUCCAGUUUUCCCAGG AAUCCCUU	401	*miR-145-1; miR-145-2*
miR-146	UGAGAACUGAAUUCCA UGGGUU	402	*miR-146-1; miR-146-2*
miR-147	GUGUGUGGAAAUGCU UCUGC	403	*miR-147*
miR-148a	UCAGUGCACUACAGAA CUUUGU	404	*miR-148a (miR-148)*
miR-148b	UCAGUGCAUCACAGAA CUUUGU	405	*miR-148b*
miR-149	UCUGGCUCCGUGUCUU CACUCC	406	*miR-149*
miR-150	UCUCCCAACCCUUGUA CCAGUG	407	*miR-150-1; miR-150-2*
miR-151	ACUAGACUGAAGCUCC UUGAGG	408	*miR-151*

(continued)

Mature miRNA Name	Mature miRNA Sequence (5' to 3')	SEQ ID NO.	Corresponding precursor microRNA (s); see Table 1a
miR-152	UCAGUGCAUGACAGAACUUGG	409	*miR-152-1; miR-152-2*
miR-153	UUGCAUAGUCACAAAAGUGA	410	*miR-153-1-1; miR-153-1-2; miR-153-2-1; miR-153-2-2*
miR-154	UAGGUUAUCCGUGUUGCCUUCG	411	*miR-154-1; miR-154-2*
*miR-154**	AAUCAUACACGGUUGACCUAUU	412	*miR-154-1; miR-154-2*
miR-155	UUAAUGCUAAUCGUGAUAGGGG	413	*miR-155*
miR-181a	AACAUUCAACGCUGUCGGUGAGU	414	*miR-181a*
miR-181b	AACAUUCAUUGCUGUCGGUGGGUU	415	*miR-181b-1; miR-181b-2*
miR-181c	AACAUUCAACCUGUCGGUGAGU	416	*miR-181c*
miR-182	UUUGGCAAUGGUAGAACUCACA	417	*miR-182; miR-182as*
*miR-182**	UGGUUCUAGACUUGCCAACUA	418	*miR-182; miR-182as*
miR-183	UAUGGCACUGGUAGAAUUCACUG	419	*miR-183*
miR-184	UGGACGGAGAACUGAUAAGGGU	420	*miR-184-1; miR-184-2*
miR-185	UGGAGAGAAAGGCAGUUC	421	*miR-185-1; miR-185-2*
miR-186	CAAAGAAUUCUCCUUUUGGGCUU	422	*miR-186-1; miR-186-2*
miR-187	UCGUGUCUUGUGUUGCAGCCG	423	*miR-187*
miR-188	CAUCCCUUGCAUGGUGGAGGGU	424	*miR-188*
miR-189	GUGCCUACUGAGCUGAUAUCAGU	425	*miR-189-1; miR-189-2*
miR-190	UGAUAUGUUUGAUAUAUUAGGU	426	*miR-190-1; miR-190-2*
miR-191	CAACGGAAUCCCAAAAGCAGCU	427	*miR-191-1; miR-191-2*

(continued)

Mature miRNA Name	Mature miRNA Sequence (5' to 3')	SEQ ID NO.	Corresponding precursor microRNA (s); see Table 1a
miR-192	CUGACCUAUGAAUUGACAGCC	428	*miR-192*
miR-193	AACUGGCCUACAAAGUCCCAG	429	*miR-193-1; miR-193-2*
miR-194	UGUAACAGCAACUCCAUGUGGA	430	*miR-194-1; miR-194-2*
miR-195	UAGCAGCACAGAAAUAUUGGC	431	*miR-195-1; miR-195-2*
miR-196a	UAGGUAGUUUCAUGUUGUUGG	432	*miR-196a; miR-196a-2 (miR196)*
miR-196b	UAGGUAGUUUCCUGUUGUUGG	433	*miR-196b*
miR-197	UUCACCACCUUCUCCACCCAGC	434	*miR-197*
miR-198	GGUCCAGAGGGGAGAUAGG	435	*miR-198*
miR-199a	CCCAGUGUUCAGACUACCUGUUC	436	*miR-199a-1; miR-199a-2*
*miR-199a**	UACAGUAGUCUGCACAUUGGUU	437	*miR-199a-1; miR-199a-2; miR-199s; miR-199b*
miR-199b	CCCAGUGUUUAGACUAUCUGUUC	438	*miR-199b*
miR-200a	UAACACUGUCUGGUAACGAUGU	439	*miR-200a*
miR-200b	CUCUAAUACUGCCUGGUAAUGAUG	440	*miR-200b*
miR-200c	AAUACUGCCGGGUAAUGAUGGA	441	*miR-200c*
miR-202	AGAGGUAUAGGGCAUGGGAAGA	442	*miR-202*
miR-203	GUGAAAUGUUUAGGACCACUAG	443	*miR-203*
miR-204	UUCCCUUUGUCAUCCUAUGCCU	444	*miR-204*
miR-205	UCCUUCAUUCCACCGGAGUCUG	445	*miR-205*
miR-206	UGGAAUGUAAGGAAGUGUGUGG	446	*miR-206-1; miR-206-2*

(continued)

Mature miRNA Name	Mature miRNA Sequence (5' to 3')	SEQ ID NO.	Corresponding precursor microRNA (s); see Table 1a
miR-208	AUAAGACGAGCAAAAAGCUUGU	447	*miR-208*
miR-210	CUGUGCGUGUGACAGCGGCUG	448	*miR-210*
miR-211	UUCCCUUUGUCAUCCUUCGCCU	449	*miR-211*
miR-212	UAACAGUCUCCAGUCACGGCC	450	*miR-212*
miR-213	ACCAUCGACCGUUGAUUGUACC	451	*miR-213*
miR-214	ACAGCAGGCACAGACAGGCAG	452	*miR-214*
miR-215	AUGACCUAUGAAUUGACAGAC	453	*miR-215*
miR-216	UAAUCUCAGCUGGCAACUGUG	454	*miR-216*
miR-217	UACUGCAUCAGGAACUGAUUGGAU	455	*miR-217*
miR-218	UUGUGCUUGAUCUAACCAUGU	456	*miR-218-1; miR-218-2*
miR-219	UGAUUGUCCAAACGCAAUUCU	457	*miR-219; miR-219-1; miR-219-2*
miR-220	CCACACCGUAUCUGACACUUU	458	*miR-220*
miR-221	AGCUACAUUGUCUGCUGGGUUUC	459	*miR-221*
miR-222	AGCUACAUCUGGCUACUGGGUCUC	460	*miR-222*
miR-223	UGUCAGUUUGUCAAAUACCCC	461	*miR-223*
miR-224	CAAGUCACUAGUGGUUCCGUUUA	462	*miR-224*
miR-296	AGGGCCCCCCCUCAAUCCUGU	463	*miR-296*
miR-299	UGGUUUACCGUCCCACAUACAU	464	*miR-299*
miR-301	CAGUGCAAUAGUAUUGUCAAAGC	465	*miR-301*

(continued)

Mature miRNA Name	Mature miRNA Sequence (5' to 3')	SEQ ID NO.	Corresponding precursor microRNA (s); see Table 1a
miR-302a	UAAGUGCUUCCAUGUU UUGGUGA	466	*miR-302a*
*miR-302b**	ACUUUAACAUGGAAGU GCUUUCU	467	*miR-302b*
miR-302b	UAAGUGCUUCCAUGUU UUAGUAG	468	*miR-302b*
*miR-302c**	UUUAACAUGGGGGUAC CUGCUG	469	*miR-302c*
miR-302c	UAAGUGCUUCCAUGUU UCAGUGG	470	*miR-302c*
miR-302d	UAAGUGCUUCCAUGUU UGAGUGU	471	*miR-302d*
miR-320	AAAAGCUGGGUUGAG AGGGCGAA	472	*miR-320*
miR-321	UAAGCCAGGGAUUGUG GGUUC	473	*miR-321*
miR-323	GCACAUUACACGGUCG ACCUCU	474	*miR-323*
miR-324-5p	CGCAUCCCCUAGGGCA UUGGUGU	475	*miR-324*
miR-324-3p	CCACUGCCCCAGGUGC UGCUGG	476	*miR-324*
miR-325	CCUAGUAGGUGUCCAG UAAGU	477	*miR-325*
miR-326	CCUCUGGGCCCUUCCU CCAG	478	*miR-326*
miR-328	CUGGCCCUCUCUGCCC UUCCGU	479	*miR-328*
miR-330	GCAAAGCACACGGCCU GCAGAGA	480	*miR-330*
miR-331	GCCCCUGGGCCUAUCC UAGAA	481	*miR-331*
miR-335	UCAAGAGCAAUAACGA AAAAUGU	482	*miR-335*
miR-337	UCCAGCUCCUAUAUGA UGCCUUU	483	*miR-337*

(continued)

Mature miRNA Name	Mature miRNA Sequence (5' to 3')	SEQ ID NO.	Corresponding precursor microRNA (s); see Table 1a
miR-338	UCCAGCAUCAGUGAUU UUGUUGA	484	*miR-338*
miR-339	UCCCUGUCCUCCAGGA GCUCA	485	*miR-339*
miR-340	UCCGUCUCAGUUACUU UAUAGCC	486	*miR-340*
miR-342	UCUCACACAGAAAUCG CACCCGUC	487	*miR-342*
miR-345	UGCUGACUCCUAGUCC AGGGC	488	*miR-345*
miR-346	UGUCUGCCCGCAUGCC UGCCUCU	489	*miR-346*
miR-367	AAUUGCACUUUAGCAA UGGUGA	490	*miR-367*
miR-368	ACAUAGAGGAAAUUCC ACGUUU	491	*miR-368*
miR-369	AAUAAUACAUGGUUG AUCUUU	492	*miR-369*
miR-370	GCCUGCUGGGGUGGAA CCUGG	493	*miR-370*
miR-371	GUGCCGCCAUCUUUUG AGUGU	494	*miR-371*
miR-372	AAAGUGCUGCGACAUU UGAGCGU	495	*miR-372*
*miR-373**	ACUCAAAAUGGGGGCG CUUUCC	496	*miR-373*
miR-373	GAAGUGCUUCGAUUUU GGGGUGU	497	*miR-373*
miR-374 .	UUAUAAUACAACCUGA UAAGUG	498	*miR-374*

[0061] The present invention encompasses methods of diagnosing or prognosticating whether a subject has, or is at risk for developing, a cancer and/or myeloproliferative disorder. The methods comprise determining the level of at least one miR gene product in a sample from the subject and comparing the level of the miR gene product in the sample to a control. As used herein, a "subject" can be any mammal that has, or is suspected of having, a cancer and/or myeloproliferative disorder. In a preferred embodiment, the subject is a human who has, or is suspected of having, a cancer, myeloproliferative disorder and/or a platelet disorder.

[0062] The level of at least one miR gene product can be measured in cells of a biological sample obtained from the subject. For example, a tissue sample can be removed from a subject suspected of having cancer and/or a myeloproliferative disorder by conventional biopsy techniques. In another embodiment, a blood sample can be removed from the subject, and white blood cells can be isolated for DNA extraction by standard techniques. In one embodiment, the blood

or tissue sample is obtained from the subject prior to initiation of radiotherapy, chemotherapy or other therapeutic treatment. A corresponding control tissue or blood sample, or a control reference sample (e.g., obtained from a population of control samples), can be obtained from unaffected tissues of the subject, from a normal human individual or population of normal individuals, or from cultured cells corresponding to the majority of cells in the subject's sample. The control tissue or blood sample can then processed along with the sample from the subject, so that the levels of miR gene product produced from a given miR gene in cells from the subject's sample can be compared to the corresponding miR gene product levels from cells of the control sample. Alternatively, a reference sample can be obtained and processed separately (e.g., at a different time) from the test sample and the level of a miR gene product produced from a given miR gene in cells from the test sample can be compared to the corresponding miR gene product level from the reference sample.

[0063] In one embodiment, the level of the at least one miR gene product in the test sample is greater than the level of the corresponding miR gene product in the control sample (i.e., expression of the miR gene product is "upregulated"), As used herein, expression of a miR gene product is "upregulated" when the amount of miR gene product in a cell or tissue sample from a subject is greater than the amount of the same gene product in a control (e.g., a reference standard, a control cell sample, a control tissue sample). In another embodiment, the level of the at least one miR gene product in the test sample is less than the level of the corresponding miR gene product in the control sample (i.e., expression of the miR gene product is "downregulated"). As used herein, expression of a miR gene is "downregulated" when the amount of miR gene product produced from that gene in a cell or tissue sample from a subject is less than the amount produced from the same gene in a control cell or tissue sample. The relative miR gene expression in the control and normal samples can be determined with respect to one or more RNA expression standards. The standards can comprise, for example, a zero miR gene expression level, the miR gene expression level in a standard cell line, the miR gene expression level in unaffected tissues of the subject, or the average level of miR gene expression previously obtained for a population of normal human controls (e.g., a control reference standard).

[0064] An alteration (*i.e.,* an increase or decrease) in the level of a miR gene product in the sample obtained from the subject, relative to the level of a corresponding miR gene product in a control sample, is indicative of the presence of cancer and/or a myeloproliferative disorder in the subject. In one embodiment, the level of the at least one miR gene product in the test sample is greater than the level of the corresponding miR gene product in the control sample. miR gene products having higher expression levels in cancer cell lines (e.g., AMKL cell lines) than control cells (e.g., *in vitro* $CD34^+$-differentiated megakaryocytes) are described and exemplified herein (see, e.g., Example 5). In one embodiment, the at least one miR gene product is selected from the group consisting of miR-101, miR-126, miR-99a, miR-99-prec, miR-106, miR-339, miR-99b, miR-149, miR-33, miR-135, miR-20 and combinations thereof In another embodiment, the at least one miR gene product is selected from the group consisting of miR-101, miR-126, miR-106, miR-20 and nuR-135 and combinations thereof. In yet another embodiment, the at least one miR gene product is selected from the group consisting of miR-106, miR-20 and miR-135 and combinations thereof. As described and exemplified herein, the increased expression of such miR gene products discriminates cancerous cells from corresponding non-cancerous cells.

[0065] As described herein, the diagnostic and prognostic methods of the invention can be used to diagnose or prognosticate cancers and/or myeloproliferative disorders. In particular embodiments, the diagnostic and prognostic methods are used to diagnose or prognosticate a cancer in a subject, tissue sample, cell sample or fluid sample. The diagnostic and prognostic methods can be used to diagnose or prognosticate any type of cancer. In particular embodiments, the diagnostic and prognostic methods can be used to diagnose or prognosticate a leukemia. In one embodiment, the leukemia that is diagnosed or prognosticated is acute myeloid leukemia (e.g., acute megakaryoblastic leukemia). In other embodiments, the diagnostic and prognostic methods can be used to diagnose or prognosticate multiple myeloma.

[0066] The diagnostic and prognostic methods of the invention can also be used to diagnose or prognosticate hematologic malignancies (e.g., myeloproliferative disorders). In one embodiment, the myeloproliferative disorder that is diagnosed or prognosticated is selected from the group consisting of essential thrombocytemia (ET), polycythemia vera (PV), myelodisplasia, myelofibrosis (e.g., agnogenic myeloid metaplasia (AMM) (also referred to as idiopathic myelofibrosis)) and chronic myelogenous leukemia (CML).

[0067] In particular embodiments, the diagnostic, prognostic and therapeutic methods of the invention can also be used to diagnose, prognosticate and/or treat platelet disorders (e.g., inherited platelet disorders). For example, the diagnostic, prognostic and therapeutic methods can be used to diagnose, prognosticate and/or treat defects in platelet-vessel wall interactions (i.e., disorders of adhesion). Such adhesion disorders include, e.g., von Willebrand disease (deficiency or defect in plasma vWF) and Bernard-Soulier syndrome (deficiency or defect in GPIb). In other embodiments, the diagnostic, prognostic and therapeutic methods can be used to diagnose, prognosticate and/or treat defects in platelet-platelet interaction (i.e., disorders of aggregation). Such aggregation disorders include, e.g., congenital afibrinogenemia (deficiency of plasma fibrinogen) and glanzmann thrombasthenia (deficiency or defect in GPIIb-IIIa). In other embodiments, the diagnostic, prognostic and therapeutic methods can be used to diagnose, prognosticate and/or treat disorders of platelet secretion and abnormalities of granules. Such disorders of platelet secretion and abnormalities of

granules include, e.g., storage pool deficiency and Quebec platelet disorder. In yet other embodiments, the diagnostic, prognostic and therapeutic methods can be used to diagnose, prognosticate and/or treat disorders of platelet secretion and signal transduction (primary secretion defects). Such primary secretion defects include, e.g., defects in platelet-agonist interaction (receptor defects) (e.g., thromboxane A_2, collagen, ADP, epinephrine), defects in G-protein activation (e.g., Gαq deficiency, Gas abnormalities, Gαi deficiency), defects in phosphatidylinositol metabolism (e.g., phospholipase C-2 deficiency), defects in calcium mobilization, defects in protein phosphorylation (pleckstrin) PKC-y deficiency, and abnormalities in arachidonic acid pathways and thromboxane synthesis (e.g., cyclooxygenase deficiency, thromboxane synthase deficiency). In other embodiments, the diagnostic, prognostic and therapeutic methods can be used to diagnose, prognosticate and/or treat defects in cytoskeletal regulation (e.g., Wiskott-Aldrich syndrome). In still other embodiments, the diagnostic, prognostic and therapeutic methods can be used to diagnose, prognosticate and/or treat disorders of platelet coagulant-protein interaction (membrane phospholipid defects) (e.g., Scott syndrome). Other platelet disorders (e.g., inherited platelet disorders) can also be diagnosed, prognosticated and/or treated using the methods of the invention.

[0068] The invention also provides methods of determining the prognosis of a subject with cancer and/or a myeloproliferative disorder. In this method, the level of at least one miR genes product, which is associated with a particular prognosis in cancer and/or a myeloproliferative disorder (e.g., a good or positive prognosis, a poor or adverse prognosis), is measured in a test sample from the subject. An alteration (e.g., an increase, a decrease) in the level of the miR gene product in the test sample, relative to the level of a corresponding miR gene product in a control sample, is indicative of the subject having a cancer and/or myeloproliferative disorder with a particular prognosis. In one embodiment, the miR gene product is associated with an adverse (i.e., poor) prognosis. Examples of an adverse prognosis include, but are not limited to, low survival rate and rapid disease progression. In one embodiment, the level of the at least one miR gene product in the test sample is greater than the level of the corresponding miR gene product in a control sample (i.e., it is upregulated). In a particular embodiment, the at least one miR gene product that is upregulated is selected from the group consisting of miR-101, miR-126, miR-99a, miR-99-prec, miR-106, miR-339, miR-99b, miR-149, miR-33, miR-135, miR-20 and combinations thereof. In another embodiment, the at least one miR gene product that is upregulated is selected from the group consisting of miR-101, miR-126, miR-106, miR-20 and miR-135 and combinations thereof In yet another embodiment, the at least one miR gene product that is upregulated is selected from the group consisting of miR-106, miR-20 and miR-135 and combinations thereof The increased expression of such miR gene products can correlate with an adverse prognosis and the severity of a subject's cancer and/or myeloproliferative disorder.

[0069] In certain embodiments of the diagnostic and prognostic methods described herein, the level of the at least one miR gene product is measured by reverse transcribing RNA from a test sample obtained from the subject to provide a set of target oligodeoxynucleotides, hybridizing the target oligodeoxynucleotides to a microarray that comprises miRNA-specific probe oligonucleotides to provide a hybridization profile for the test sample, and comparing the test sample hybridization profile to a hybridization profile generated from a control sample.

[0070] Identification of targets of particular miR gene products (e.g., those miR gene products exhibiting upregulated or downregulated expression relative to a control sample) can aid in elucidating mechanisms of action of microRNAs. As described and exemplified herein, particular targets and putative targets of select microRNAs were identified (see, e.g., Tables 2, 3 and 5 and Exemplification). For example, the transcription factor MAFB was identified as a target of mi-130a (Example 2). Similarly, HOXA1 was identified as a target of miR-10a (Example 5). For both miRs, direct interaction of the miR with the 3' UTR of its respective target was demonstrated (Examples 2 and 5). Moreover, an inverse relation in the expression of the miR and its respective target were demonstrated. Thus, expression of pre-miR-130a resulted in decreased expression of MAFB (see, e.g., FIG. 2C) while expression of pre-miR-10a resulted in decreased expression of HOXA1 (see, e.g., FIGS. 3C, 3F and 3G). Thus, in one embodiment, expression of target genes of particular microRNAs (e.g., those listed in Tables 2, 3 and 5) can be used to diagnose cancer and/or a myeloproliferative disorder. Such target genes display inverse expression to the respective miR that targets it. One of skill in the art can measure the expression levels of any of these target genes using known methods and/or methods described herein for measuring the expression levels of microRNAs (e.g., quantitative or semi-quantitative RT-PCR, Northern blot analysis, solution hybridization detection, microarray analysis), without undue experimentation. In particular embodiments, the target gene that is measured is MAFB or HOXA1.

[0071] The level of the at least one miR gene product can be measured using a variety of techniques that are well known to those of skill in the art (e.g., quantitative or semi-quantitative RT-PCR, Northern blot analysis, solution hybridization detection). In a particular embodiment, the level of at least one miR gene product is measured by reverse transcribing RNA from a test sample obtained from the subject to provide a set of target oligodeoxynucleotides, hybridizing the target oligodeoxynucleotides to one or more miRNA-specific probe oligonucleotides (e.g., a microarray that comprises miRNA-specific probe oligonucleotides) to provide a hybridization profile for the test sample, and comparing the test sample hybridization profile to a hybridization profile generated from a control sample. An alteration in the signal of at least one miRNA in the test sample relative to the control sample is indicative of the subject either having, or being at risk for developing cancer and/or a myeloproliferative disorder. In one embodiment, the signal of at least one miRNA is

upregulated, relative to the signal generated from the control sample. In another embodiment, the signal of at least one miRNA is downregulated, relative to the signal generated from the control sample. In a particular embodiment, the microarray comprises miRNA-specific probe oligonucleotides for a substantial portion of all known human miRNAs (e.g., the miRNAs listed in Tables 1a and 1b plus other known or discovered miRNAs). In a further embodiment, the microarray comprises miRNA-specific probe oligonucleotides for one or more miRNAs selected from the group consisting of miR-101, miR-126, miR-99a, miR-99-prec, miR-106, miR-339, miR-99b, miR-149, miR-33, miR-135, miR-20 and a combination thereof. In one embodiment, the microarray comprises miRNA-specific probe oligonucleotides for one or more miRNAs selected from the group consisting of miR-101, miR-126, miR-106, miR-20, miR-135 and a combination thereof.

[0072] The microarray can be prepared from gene-specific oligonucleotide probes generated from known miRNA sequences, The array may contain two different oligonucleotide probes for each miRNA, one containing the active, mature sequence and the other being specific for the precursor of the miRNA. The array may also contain controls, such as one or more mouse sequences differing from human orthologs by only a few bases, which can serve as controls for hybridization stringency conditions. tRNAs and other RNAs (e.g., rRNAs, mRNAs) from both species may also be printed on the microchip, providing an internal, relatively stable, positive control for specific hybridization. One or more appropriate controls for non-specific hybridization may also be included on the microchip. For this purpose, sequences are selected based upon the absence of any homology with any known miRNAs.

[0073] The microarray may be fabricated using techniques known in the art. For example, probe oligonucleotides of an appropriate length, e.g., 40 nucleotides, are 5'-amine modified at position C6 and printed using commercially available microarray systems, e.g., the GanaMachine OmniGrid™ 100 Microarrayer and Amersham CodeLink™ activated slides. Labeled cDNA oligomer corresponding to the target RNAs is prepared by reverse transcribing the target RNA with labeled primer. Following first strand synthesis, the RNA/DNA hybrids are denatured to degrade the RNA templates. The labeled target cDNAs thus prepared are then hybridized to the microarray chip under hybridizing conditions, e.g., 6X SSPE/30% formamide at 25˚C for 18 hours, followed by washing in 0.75X TNT at 37˚C for 40 minutes. At positions on the array where the immobilized probe DNA recognizes a complementary target cDNA in the sample, hybridization occurs. The labeled target cDNA marks the exact position on the array where binding occurs, allowing automatic detection and quantification. The output consists of a list of hybridization events, indicating the relative abundance of specific cDNA sequences, and therefore the relative abundance of the corresponding complementary miRs, in the patient sample. According to one embodiment, the labeled cDNA oligomer is a biotin-labeled cDNA, prepared from a biotin-labeled primer. The microarray is then processed by direct detection of the biotin-containing transcripts using, e.g., Streptavidin-Alexa647 conjugate, and scanned utilizing conventional scanning methods. Image intensities of each spot on the array are proportional to the abundance of the corresponding miR in the patient sample.

[0074] The use of the array has several advantages for miRNA expression detection. First, the global expression of several hundred genes can be identified in the same sample at one time point. Second, through careful design of the oligonucleotide probes, expression of both mature and precursor molecules can be identified. Third, in comparison with Northern blot analysis, the chip requires a small amount of RNA, and provides reproducible results using 2.5 μg of total RNA. The relatively limited number of miRNAs (a few hundred per species) allows the construction of a common microarray for several species, with distinct oligonucleotide probes for each. Such a tool would allow for analysis of trans-species expression for each known miR under various conditions.

[0075] In addition to use for quantitative expression level assays of specific miRs, a microchip containing miRNA-specific probe oligonucleotides corresponding to a substantial portion of the miRNome, preferably the entire miRNome, may be employed to carry out miR gene expression profiling, for analysis ofmiR expression patterns. Distinct miR signatures can be associated with established disease markers, or directly with a disease state.

[0076] According to the expression profiling methods described herein, total RNA from a sample from a subject suspected of having a cancer and/or a myeloproliferative disorder is quantitatively reverse transcribed to provide a set of labeled target oligodeoxynucleotides complementary to the RNA in the sample. The target oligodeoxynucleotides are then hybridized to a microarray comprising miRNA-specifc probe oligonucleotides to provide a hybridization profile for the sample. The result is a hybridization profile for the sample representing the expression pattern of miRNA in the sample. The hybridization profile comprises the signal from the binding of the target oligodeoxynucleotides from the sample to the miRNA-specific probe oligonucleotides in the microarray. The profile may be recorded as the presence or absence of binding (signal vs. zero signal). More preferably, the profile recorded includes the intensity of the signal from each hybridization. The profile is compared to the hybridization profile generated from a normal (e.g., noncancerous, non-myeloproliferative disorder) control sample or reference sample. An alteration in the signal is indicative of the presence of, or propensity to develop, cancer in the subject.

[0077] Other techniques for measuring miR gene expression are also within the skill in the art, and include various techniques for measuring rates of RNA transcription and degradation.

[0078] The invention also provides methods of diagnosing whether a subject has, or is at risk for developing, a cancer and/or myeloproliferative disorder with an adverse prognosis. In this method, the level of at least one miR gene product, which is associated with an adverse prognosis in a cancer and/or myeloproliferative disorder, is measured by reverse

transcribing RNA from a test sample obtained from the subject to provide a set of target oligodeoxynucleotides. The target oligodeoxynucleotides are then hybridized to one or more miRNA-specific probe oligonucleotides (e.g., a microarray that comprises miRNA-specific probe oligonucleotides) to provide a hybridization profile for the test sample, and the test sample hybridization profile is compared to a hybridization profile generated from a control sample. An alteration in the signal of at least one miRNA in the test sample relative to the control sample is indicative of the subject either having, or being at risk for developing, a cancer and/or myeloproliferative disorder with an adverse prognosis. miRs suitable for use in this method include, e.g" those that are upregulated in cancerous cells (e.g., AMKL cells).

[0079] In particular embodiments of the diagnostic, prognostic and therapeutic methods of the invention, as well as the pharmaceutical compositions of the invention, the miR gene product is not one or more of let7a-2, let-7c, let-7g, let-7i, miR-7-2, miR-7-3, miR-9, miR-9-1, miR-10a, miR-15a, miR-15b, miR-16-1, miR-16-2, miR-17-5p, miR-20a, miR-21, miR-24-1, miR-24-2, miR-25, miR-29b-2, miR-30, miR-30a-5p, miR-30c, miR-30d, miR-31, miR-32, miR-34, miR-34a, miR-34a prec, miR-34a-1, miR-34a-2, miR-92-2, miR-96, miR-99a, miR-99b pree, miR-100, miR-103, miR-106a, miR-107, miR-123, miR-124a-1, miR-125b-1, miR-125b-2, miR-126*, miR-127, miR-128b, miR-129, miR-129-1/2 prec, miR-132, miR-135-1, miR-136, miR-137, miR-141, miR-142-as, miR-143, miR-146, miR-148, miR-149, miR-153, miR-155, miR 159-1, miR-181, miR-181b-1, miR-182, miR-186, miR-191, miR-192, miR-195, miR-196-1, miR-196-1 prec, miR-196-2, miR-199a-1, miR-199a-2, miR-199b, miR-200b, miR-202, miR-203, miR-204, miR-205, miR-21 0, miR-211, miR-212, miR-214, miR-215, miR-217, miR-221 and/or miR-223.

[0080] As described herein, the level of a miR gene product in a sample can be measured using any technique that is suitable for detecting RNA expression levels in a biological sample. Suitable techniques (e.g., Northern blot analysis, RT-PCR, *in situ* hybridization) for determining RNA expression levels in a biological sample (e.g., cells, tissues) are well known to those of skill in the art. In a particular embodiment, the level of at least one miR gene product is detected using Northern blot analysis. For example, total cellular RNA can be purified from cells by homogenization in the presence of nucleic acid extraction buffer, followed by centrifugation. Nucleic acids are precipitated, and DNA is removed by treatment with DNase and precipitation. The RNA molecules are then separated by gel electrophoresis on agarose gels according to standard techniques, and transferred to nitrocellulose filters. The RNA is then immobilized on the filters by heating. Detection and quantification of specific RNA is accomplished using appropriately labeled DNA or RNA probes complementary to the RNA in question. See, for example, Molecular Cloning: A Laboratory Manual, J. Sambrook et al., eds., 2nd edition, Cold Spring Harbor Laboratory Press, 1989, Chapter 7, the entire disclosure of which is incorporated by reference.

[0081] Suitable probes (e.g., DNA probes, RNA probes) for Northern blot hybridization of a given miR gene product can be produced from the nucleic acid sequences provided in Table 1a and Table 1b and include, but are not limited to, probes having at least about 70%, 75%, 80%, 85%, 90%, 95%, 98% or 99% complementarity to a miR gene product of interest, as well as probes that have complete complementarity to a miR gene product of interest. Methods for preparation of labeled RNA and RNA probes, and the conditions for hybridization thereof to target nucleotide sequences, are described in Molecular Cloning: A Laboratory Manual, J. Sambrook et al., eds., 2nd edition, Cold Spring Harbor Laboratory Press, 1989, Chapters 10 and 11, the disclosures of which are incorporated herein by reference.

[0082] For example, the nucleic acid probe can be labeled with, e.g., a radionuclide, such as ^{3}H, ^{32}P, ^{33}P, ^{14}C, or ^{35}S; a heavy metal; a ligand capable of functioning as a specific binding pair member for a labeled ligand (e.g., biotin, avidin or an antibody); a fluorescent molecule; a chemiluminescent molecule; an enzyme or the like.

[0083] Probes can be labeled to high specific activity by either the nick translation method of Rigby et al. (1977), J. Mol. Biol, 113:237-251 or by the random priming method of Fienberg et al. (1983), Anal. Biochem. 132:6-13, the entire disclosures ofwhich are incorporated herein by reference. The latter is the method of choice for synthesizing ^{32}P-labeled probes of high specific activity from single-stranded DNA or from RNA templates. For example, by replacing preexisting nucleotides with highly radioactive nucleotides according to the nick translation method, it is possible to prepare ^{32}P-labeled nucleic acid probes with a specific activity well in excess of 10^{8} cpm/microgram. Autoradiographic detection of hybridization can then be performed by exposing hybridized filters to photographic film. Densitometric scanning of the photographic films exposed by the hybridized filters provides an accurate measurement of m iR gene transcript levels. Using another approach, miR gene transcript levels can be quantified by computerized imaging systems, such as the Molecular Dynamics 400-B 2D Phosphorimager available from Amersham Biosciences, Piscataway, NJ.

[0084] Where radionuclide labeling of DNA or RNA probes is not practical, the random-primer method can be used to incorporate an analogue, for example, the dTTP analogue 5-(N-(N-biotinyl-epsilon-aminocaproyl)-3-aminoallyl)deoxyuridine triphosphate, into the probe molecule. The biotinylated probe oligonucleotide can be detected by reaction with biotin-binding proteins, such as avidin, streptavidin and antibodies (e.g., anti-biotin antibodies) coupled to fluorescent dyes or enzymes that produce color reactions.

[0085] In addition to Northern and other RNA hybridization techniques, determining the levels of RNA transcripts can be accomplished using the technique of *in situ* hybridization. This technique requires fewer cells than the Northern blotting technique and involves depositing whole cells onto a microscope cover slip and probing the nucleic acid content of the cell with a solution containing radioactive or otherwise labeled nucleic acid (e.g., cDNA or RNA) probes. This

technique is particularly well-suited for analyzing tissue biopsy samples from subjects. The practice of the *in situ* hybridization technique is described in more detail in U.S. Patent No. 5,427,916, the entire disclosure of which is incorporated herein by reference. Suitable probes for *in situ* hybridization of a given miR gene product can be produced from the nucleic acid sequences provided in Table 1a and Table 1b, and include, but are not limited to, probes having at least about 70%, 75%, 80%, 85%, 90%, 95%, 98% or 99% complementarity to a miR gene product of interest, as well as probes that have complete complementarity to a miR gene product of interest, as described above.

[0086] The relative number of miR gene transcripts in cells can also be determined by reverse transcription of miR gene transcripts, followed by amplification of the reverse-transcribed transcripts by polymerase chain reaction (RT-PCR), for example, as exemplified herein. The levels of miR gene transcripts can be quantified in comparison with an internal standard, for example, the level ofmRNA from a "housekeeping" gene present in the same sample. A suitable "housekeeping" gene for use as an internal standard includes, e.g., U6 small nuclear RNA, myosin or glyceraldehyde-3-phosphate dehydrogenase (G3PDH). Methods for performing quantitative and semi-quantitative RT-PCR, and variations thereof, are well known to those of skill in the art.

[0087] In some instances, it may be desirable to simultaneously determine the expression level of a plurality of different miR gene products in a sample. In other instances, it may be desirable to determine the expression level of the transcripts of all known miR genes correlated with a cancer and/or myeloproliferative disorder. Assessing cancer-specific expression levels for hundreds of miR genes or gene products is time consuming and requires a large amount of total RNA (e.g., at least 20 μg for each Northern blot) and autoradiographic techniques that require radioactive isotopes.

[0088] To overcome these limitations, an oligolibrary, in microchip format (i.e., a microarray), may be constructed containing a set of oligonucleotide (e.g., oligodeoxynucleotide) probes that are specific for a set of miR genes. Using such a microarray, the expression level of multiple microRNAs in a biological sample can be determined by reverse transcribing the RNAs to generate a set of target oligodeoxynucleotides, and hybridizing them to probe the oligonucleotides on the microarray to generate a hybridization, or expression, profile. The hybridization profile of the test sample can then be compared to that of a control sample to determine which microRNAs have an altered expression level in cancer cells and/or cells exhibiting a myeloproliferative disorder. As used herein, "probe oligonucleotide" or "probe oligodeoxynucleotide" refers to an oligonucleotide that is capable of hybridizing to a target oligonucleotide. "Target oligonucleotide" or "target oligodeoxynucleotide" refers to a molecule to be detected (e.g., via hybridization). By "miR-specific probe oligonucleotide" or "probe oligonucleotide specific for a miR" is meant a probe oligonucleotide that has a sequence selected to hybridize to a specific miR gene product, or to a reverse transcript of the specific miR gene product.

[0089] An "expression profile" or "hybridization profile" of a particular sample is essentially a fingerprint of the state of the sample; while two states may have any particular gene similarly expressed, the evaluation of a number of genes simultaneously allows the generation of a gene expression profile that is unique to the state of the cell. That is, normal tissue, cell or fluid samples may be distinguished from corresponding cancerous and/or myeloproliferative disorder-exhibiting tissue, cell or fluid samples. Within cancerous and/or myeloproliferative disorder-exhibiting tissue, cell or fluid samples, different prognosis states (for example, good or poor long term survival prospects) may be determined. By comparing expression profiles of cancerous and/or myeloproliferative disorder-exhibiting tissue, cell or fluid samples in different states, information regarding which genes are important (including both upregulation and downregulation of genes) in each of these states is obtained. The identification of sequences that are differentially expressed in cancerous and/or myeloproliferative disorder-exhibiting tissue, cell or fluid samples, as well as differential expression resulting in different prognostic outcomes, allows the use of this information in a number of ways. For example, a particular treatment regime may be evaluated (e.g., to determine whether a chemotherapeutic drug acts to improve the long-term prognosis in a particular subject). Similarly, diagnosis may be done or confirmed by comparing samples from a subject with known expression profiles. Furthermore, these gene expression profiles (or individual genes) allow screening of drug candidates that suppress the cancer and/or myeloproliferative disorder expression profile or convert a poor prognosis profile to a better prognosis profile.

[0090] Without wishing to be bound by any one theory, it is believed that alterations in the level of one or more miR gene products in cells can result in the deregulation of one or more intended targets for these miRs, which can lead to aberrant megakaryocytic differentiation and/or the formation of cancer, a myeloproliferative disorder and/or a platelet disorder. Therefore, altering the level of the miR gene product (e.g., by decreasing the level of a miR that is upregulated in cancerous and/or myeloproliferative disorder-exhibiting cells, by increasing the level of a miR that is downregulated in cancerous and/or myeloproliferative disorder-exhibiting cells) may successfully treat the cancer, myeloproliferative disorder and/or platelet disorder.

[0091] Accordingly, the present invention encompasses methods of treating a cancer and/or myeloproliferative disorder in a subject, wherein at least one miR gene product is deregulated (e.g., downregulated, upregulated) in the cells (e.g., cancerous cells and/or myeloproliferative disorder-exhibiting cells) of the subject. In one embodiment, the level of at least one miR gene product in a test sample (e.g., a sample comprising cancerous and/or myeloproliferative disorder-exhibiting tissues, cells or fluid) is greater than the level of the corresponding miR gene product in a control or reference sample. In another embodiment, the level of at least one miR gene product in a test sample (e.g., a sample comprising

cancerous and/or myeloproliferative disorder-exhibiting tissues, cells or fluid) is less than the level of the corresponding miR gene product in a control sample. When the at least one isolated miR gene product is downregulated in the test sample (e.g., a sample comprising cancerous and/or myeloproliferative disorder-exhibiting tissues, cells or fluid), the method comprises administering an effective amount of the at least one isolated miR gene product, or an isolated variant or biologically-active fragment thereof, such that proliferation of the cancerous and/or myeloproliferative disorder-exhibiting cells in the subject is inhibited. For example, when a miR gene product is downregulated in a cancer cell in a subject, administering an effective amount of an isolated miR gene product to the subject can inhibit proliferation of the cancer call, The isolated miR gene product that is administered to the subject can be identical to an endogenous wild-type miR gene product (e.g., a miR gene product shown in Table 1a or Table 1b) that is downregulated in the cancer cell or it can be a variant or biologically-active fragment thereof As defined herein, a "variant" of a miR gene product refers to a miRNA that has less than 100% identity to a corresponding wild-type miR gene product and possesses one or more biological activities of the corresponding wild-type miR gene product. Examples of such biological activities include, but are not limited to, inhibition of expression of a target RNA molecule (e.g., inhibiting translation of a target RNA molecule, modulating the stability of a target RNA, molecule, inhibiting processing of a target RNA molecule) and inhibition of a cellular process associated with cancer and/or a myeloproliferative disorder (e.g., cell differentiation, cell growth, cell death). These variants include species variants and variants that are the consequence of one or more mutations (e.g., a substitution, a deletion, an insertion) in a miR gene. In certain embodiments, the variant is at least about 70%, 75%, 80%, 85%, 90%, 95%, 98%, or 99% identical to a corresponding wild-type miR gene product.

[0092] As defined herein, a "biologically-active fragment" of a miR gene product refers to an RNA fragment of a miR gene product that possesses one or more biological activities of a corresponding wild-type miR gene product. As described above, examples of such biological activities include, but are not limited to, inhibition of expression of a target RNA molecule and inhibition of a cellular process associated with cancer and/or a myeloproliferative disorder. In certain embodiments, the biologically-active fragment is at least about 5, 7, 10, 12, 15, or 17 nucleotides in length. In a particular embodiment, an isolated miR gene product can be administered to a subject in combination with one or more additional anti-cancer treatments. Suitable anti-cancer treatments include, but are not limited to, chemotherapy, radiation therapy and combinations thereof (e.g., chemoradiation).

[0093] When the at least one isolated miR gene product is upregulated in the cancer cells, the method comprises administering to the subject an effective amount of a compound that inhibits expression of the at least one miR gene product, such that proliferation of the cancer and/or myeloproliferative disorder-exhibiting cells is inhibited. Such compounds are referred to herein as miR gene expression-inhibition compounds. Examples of suitable miR gene expression-inhibition compounds include, but are not limited to, those described herein (e.g., double-stranded RNA, antisense nucleic acids and enzymatic RNA molecules). In a particular embodiment, a miR gene expression-inhibiting compound can be administered to a subject in combination with one or more additional anti-cancer treatments. Suitable anti-cancer treatments include, but are not limited to, chemotherapy, radiation therapy and combinations thereof (e.g., chemoradiation).

[0094] As described, when the at least one isolated miR gene product is upregulated in cancer cells (e.g., AMKL cells), the method comprises administering to the subject an effective amount of at least one compound for inhibiting expression of the at least one miR gene product, such that proliferation of cancer cells is inhibited. In one embodiment, the compound for inhibiting expression of the at least one miR gene product inhibits a miR gene product selected from the group consisting of miR-101, miR-126, miR-99a, miR-99-prec, miR-106, miR-339, miR-99b, miR-149, miR-33, miR-135, miR-20 and a combination thereof. In another embodiment, the compound for inhibiting expression of the at least one miR gene product inhibits a miR gene product selected from the group consisting of miR-101, miR-126, miR-106, miR-20, miR-135 and a combination thereof. In yet another embodiment, the compound for inhibiting expression of the at least one miR gene product inhibits a miR gene product selected from the group consisting of miR-106, miR-20, miR-135 and a combination thereof

[0095] As described and exemplified herein, the transcription factor MAFB, which is upregulated in megakaryocytic differentiation, is a target of miR-130a. Moreover, an inverse relation in the expression of miR-130a and its respective target were demonstrated. Thus, expression of pre-miR-130a resulted in decreased expression of *MAFB* (see, e.g., FIG. 2C). MAFB is known to be deregulated in cancer (e.g., multiple myeloma and acute myeloid leukemia). For example, ectopic expression of MAFB has been observed in human myeloma cells carrying (14;20)(q32;q11) chromosomal translocations (Hanamura, I.. et al. (2001) Jpn. J. Cancer Res. 92(6):638-644 (2001)). Accordingly, in one embodiment, the invention is a method of treating a cancer and/or myeloproliferative disorder in a subject comprising administering an effective amount of at least one miR gene product or an isolated variant or biologically-active fragment thereof to the subject, wherein:

[0096] the cancer and/or myeloproliferative disorder is associated with overexpression of a MAFB gene product; and

[0097] the at least one miR gene product binds to, and decreases expression of, the MAFB gene product.

[0098] In one embodiment, the at least one miR gene product or isolated variant or biologically-active fragment thereof comprises a nucleotide sequence that is complementary to a nucleotide sequence in the MAFB gene product (e.g.,

complementary to the 3' UTR of MAFB). In a particular embodiment, the at least one miR gene product is miR-130a or an isolated variant or biologically-active fragment thereof.

[0099] Also as described and exemplified herein, mRNA of HOXA1, one of the members of the HOX family of proteins, is upregulated 7-fold in megakaryocytic differentiation (see, e.g., Example 4). Moreover, HOXA1 is a target of miR-10a and its expression is inversely related to the expression af miR-10a. Thus, expression of pre-miR-10a resulted in decreased expression of HOXA1 (see, e.g., FIGS. 3C, 3F and 3G). HOXA1. Expression of HOXA1 has been demonstrated to be sufficient to result in the oncogenic transformation of immortalized human mammary epithelial cells with aggressive *in vivo* tumor formation (Zhang, X., et al., (2002) J. Biol. Chem. 278(9):7580-7590). Further, forced expression of HOXA1 in mammary carcinoma cells, in a Bcl-2-dependent manner, resulted in a dramatic enhancement of anchorage-independent proliferation and colony formation in soft agar. *Id.* Accordingly, in one embodiment, the invention is a method of treating a cancer and/or myeloproliferative disorder in a subject comprising administering an effective amount of at least one miR gene product or an isolated variant or biologically-active fragment thereof to the subject, wherein:

[0100] the cancer and/or myeloproliferative disorder is associated with overexpression of a HOXA1 gene product; and

[0101] the at least one miR gene product binds to, and decreases expression of, the HOXA1 gene product.

[0102] In one embodiment, the at least one miR gene product or isolated variant or biologically-active fragment thereof comprises a nucleotide sequence that is complementary to a nucleotide sequence in the HOXA1 gene product (e.g., complementary to the 3' UTR of HOXA1). In a particular embodiment, the at least one miR gene product is miR-10a or an isolated variant or biologically-active fragment thereof.

[0103] In a related embodiment, the methods of treating cancer and/or a myeloproliferative disorder in a subject additionally comprise the step of first determining the amount of at least one miR gene product in a sample from the subject, and comparing that level of the miR gene product to the level of a corresponding miR gene product in a control. If expression of the miR gene product is deregulated (e.g., downregulated, upregulated) in the sample from the subject, the methods further comprise altering the amount of the at least one miR gene product expressed in the sample from the subject. In one embodiment, the amount of the miR gene product expressed in the sample from the subject is less than the amount of the miR gene product expressed in the control, and an effective amount of the miR gene product, or an isolated variant or biologically-active fragment thereof, is administered to the subject. In another embodiment, the amount of the miR gene product expressed in the samples from the subject is greater than the amount of the miR gene product expressed in the control, and an effective amount of at least one compound for inhibiting expression of the at least one miR gene is administered to the subject. Suitable miRs and compounds that inhibit expression of miR genes include, for example, those described herein.

[0104] The terms "treat", "treating" and "treatment", as used herein, refer to ameliorating symptoms associated with a disease or condition, for example, cancer and/or a myeloproliferative disorder, including preventing or delaying the onset of the disease symptoms, and/or lessening the severity or frequency of symptoms of the disease or condition. The terms "subject", "patient" and "individual" are defined herein to include animals, such as mammals, including, but not limited to, primates, cows, sheep, goats, horses, dogs, cats, rabbits, guinea pigs, rats, mice or other bovine, ovine, equine, canine, feline, rodent, or murine species. In a preferred embodiment, the animal is a human.

[0105] As used herein, an "effective amount" of an isolated miR gene product is an amount sufficient to inhibit proliferation of cells (e.g., cancerous cells, cells exhibiting a myeloproliferative disorder) in a subject suffering from cancer and/or a myeloproliferative disorder. One skilled in the art can readily determine an effective amount of a miR gene product to be administered to a given subject, by taking into account factors, such as the size and weight of the subject; the extent of disease penetration; the age, health and sex of the subject; the route of administration; and whether the administration is regional or systemic.

[0106] For example, an effective amount of an isolated miR gene product can be based on the approximate weight of a tumor mass to be treated. The approximate weight of a tumor mass can be determined by calculating the approximate volume of the mass, wherein one cubic centimeter of volume is roughly equivalent to one gram. An effective amount of the isolated miR gene product based on the weight of a tumor mass can be in the range of about 10-500 micrograms/gram of tumor mass. In certain embodiments, the tumor mass can be at least about 10 micrograms/gram of tumor mass, at least about 60 micrograms/gram of tumor mass or at least about 100 micrograms/gram of tumor mass.

[0107] An effective amount of an isolated miR gene product can also be based on the approximate or estimated body weight of a subject to be treated. Preferably, such effective amounts are administered parenterally or enterally, as described herein. For example, an effective amount of the isolated miR gene product that is administered to a subject can range from about 5 - 3000 micrograms/kg of body weight, from about 700 - 1000 micrograms/kg of body weight, or greater than about 1000 micrograms/kg of body weight,

[0108] One skilled in the art can also readily determine an appropriate dosage regimen for the administration of an isolated miR gene product to a given subject. For example, a miR gene product can be administered to the subject once (e.g., as a single injection or deposition). Alternatively, a miR gene product can be administered once or twice daily to a subject for a period of from about three to about twenty-eight days, more particularly from about seven to about ten days. In a particular dosage regimen, a miR gene product is administered once a day for seven days. Where a dosage

regimen comprises multiple administrations, it is understood that the effective amount of the miR- gene product administered to the subject can comprise the total amount of gene product administered over the entire dosage regimen.

[0109] As used herein, an "isolated" miR gene product is one that is synthesized, or altered or removed from the natural state through human intervention. For example, a synthetic miR gene product, or a miR gene product partially or completely separated from the coexisting materials of its natural state, is considered to be "isolated." An isolated miR gene product can exist in a substantially-purified form, or can exist in a cell into which the miR gene product has been delivered. Thus, a miR gene product that is deliberately delivered to, or expressed in, a cell is considered an "isolated" miR gene product. A miR gene product produced inside a cell from a miR precursor molecule is also considered to be an "isolated" molecule. According to the invention, the isolated miR gene products described herein can be used for the manufacture of a medicament for treating cancer and/or a myeloproliferative disorder in a subject (e.g., a human).

[0110] Isolated miR gene products can be obtained using a number of standard techniques. For example, the miR gene products can be chemically synthesized or recombinantly produced using methods known in the art. In one embodiment, miR gene products are chemically synthesized using appropriately protected ribonucleoside phosphoramidites and a conventional DNA/RNA synthesizer. Commercial suppliers of synthetic RNA molecules or synthesis reagents include, e.g., Proligo (Hamburg, Germany), Dharmacon Research (Lafayette, CO, U.S.A.), Pierce Chemical (part of-Perbio Science, Rockford, IL, U.S.A.), Glen Research (Sterling, VA, U.S.A.), ChemGenes (Ashland, MA, U.S.A.) and Cruachem (Glasgow, UK).

[0111] Alternatively, the miR gene products can be expressed from recombinant circular or linear DNA plasmids using any suitable promoter. Suitable promoters for expressing RNA from a plasmid include, e.g., the U6 or H1RNA pol III promoter sequences, or the cytomegalovirus promoters. Selection of other suitable promoters is within the skill in the art. The recombinant plasmids of the invention can also comprise inducible or regulatable promoters for expression of the miR gene products in cells (e.g., cancerous cells, cells exhibiting a myeloproliferative disorder).

[0112] The miR gene products that are expressed from recombinant plasmids can be isolated from cultured cell expression systems by standard techniques. The miR gene products that are expressed from recombinant plasmids can also be delivered to, and expressed directly in, cells (e.g., cancerous cells, cells exhibiting a myeloproliferative disorder). The use of recombinant plasmids to deliver the miR gene products to cells (e.g., cancerous cells, cells exhibiting a myeloproliferative disorder) is discussed in more detail below.

[0113] The miR gene products can be expressed from a separate recombinant plasmids, or they can be expressed from the same recombinant plasmid. In one embodiment, the miR gene products are expressed as RNA precursor molecules from a single plasmid, and the precursor molecules are processed into the functional miR gene product by a suitable processing system, including, but not limited to, processing systems extant within a cancer cell. Other suitable processing systems include, e.g., the *in vitro* Drosophila cell lysate system (e.g., as described in U.S. Published Patent Application No. 2002/0086356 to Tuschl et al., the entire disclosure of which is incorporated herein by reference) and the *E. coli* RNAse III system (e.g., as described in U.S. Published Patent Application No. 2004/0014113 to Yang et al., the entire disclosure of which is incorporated herein by reference).

[0114] Selection of plasmids suitable for expressing the miR gene products, methods for inserting nucleic acid sequences into the plasmid to express the gene products, and methods of delivering the recombinant plasmid to the cells of interest are within the skill in the art. See, for example, Zeng et al. (2002), Molecular Cell 9:1327-1333; Tuschl (2002), Nat. Biotechnol, 20:446-448; Brummelkamp et al. (2002), Science 296:550-553; Miyagishi et al. (2002), Nat. Biotechnol. 20:497-500; Paddison et al. (2002), Genes Dev. 16:948-958; Lee et al. (2002), Nat. Biotechnol. 20:500-505; and Paul et al. (2002), Nat. Biotechnol. 20:505-508, the entire disclosures ofwhich are incorporated herein by reference.

[0115] In one embodiment, a plasmid expressing the miR gene products comprises a sequence encoding a miR precursor RNA under the control of the CMV intermediate-early promoter. As used herein, "under the control" of a promoter means that the nucleic acid sequences encoding the miR gene product are located 3' of the promoter, so that the promoter can initiate transcription of the miR gene product coding sequences.

[0116] The miR gene products can also be expressed from recombinant viral vectors. It is contemplated that the miR gene products can be expressed from two separate recombinant viral vectors, or from the same viral vector. The RNA expressed from the recombinant viral vectors can either be isolated from cultured cell expression systems by standard techniques, or can be expressed directly in cells (e.g., cancerous cells, cells exhibiting a myeloproliferative disorder). The use of recombinant viral vectors to deliver the miR gene products to cells (e.g., cancerous cells, cells exhibiting a myeloproliferative disorder) is discussed in more detail below.

[0117] The recombinant viral vectors of the invention comprise sequences encoding the miR gene products and any suitable promoter for expressing the RNA sequences. Suitable promoters include, but are not limited to, the U6 or H1 RNA pol III promoter sequences, or the cytomegalovirus promoters. Selection of other suitable promoters is within the skill in the art. The recombinant viral vectors of the invention can also comprise inducible or regulatable promoters for expression of the miR gene products in a cancer cell.

[0118] Any viral vector capable of accepting the coding sequences for the miR gene products can be used; for example, vectors derived from adenovirus (AV); adeno-associated virus (AAV); retroviruses (*e.g.*, lentiviruses (LV), Rhabdoviruses,

murine leukemia virus); herpes virus, and the like. The tropism of the viral vectors can be modified by pseudotyping the vectors with envelope proteins or other surface antigens from other viruses, or by substituting different viral capsid proteins, as appropriate.

[0119] For example, lentiviral vectors of the invention can be pseudotyped with surface proteins from vesicular stomatitis virus (VSV), rabies, Ebola, Mokola, and the like. AAV vectors of the invention can be made to target different cells by engineering the vectors to express different capsid protein serotypes. For example, an AAV vector expressing a serotype 2 capsid on a serotype 2 genome is called AAV 2/2. This serotype 2 capsid gene in the AAV 2/2 vector can be replaced by a serotype 5 capsid gene to produce an AAV 2/5 vector. Techniques for constructing AAV vectors that express different capsid protein serotypes are within the skill in the art; *see, e.g.,* Rabinowitz, J.E., et al. (2002), J. Virol. 76:791-801, the entire disclosure of which is incorporated herein by reference.

[0120] Selection of recombinant viral vectors suitable for use in the invention, methods for inserting nucleic acid sequences for expressing RNA into the vector, methods of delivering the viral vector to the cells of interest, and recovery of the expressed RNA products are within the skill in the art. See, for example, Dornburg (1995), Gene Therapy 2: 301-310; Eglitis (1988), Biotechniques 6:608-614; Miller (1990), Hum. Gene Therapy 1:5-14; and Anderson (1998), Nature 392:25-30, the entire disclosures of which are incorporated herein by reference.

[0121] Particularly suitable viral vectors are those derived from AV and AAV. A suitable AV vector for expressing the miR gene products, a method for constructing the recombinant AV vector, and a method for delivering the vector into target cells, are described in Xia et al. (2002), Nat. Biotech. 20:1006-1010, the entire disclosure of which is incorporated herein by reference. Suitable AAV vectors for expressing the miR gene products, methods for constructing the recombinant AAV vector, and methods for delivering the vectors into target cells are described in Samulski et al. (1987), J. Virol. 61:3096-3101; Fisher et al. (1996), J. Virol., 70:520-532; Samulski et al. (1989), J. Virol. 63:3822-3826; U.S. Patent No. 5,252,479; U.S. Patent No. 5,139,941; International Patent Application No. WO 94/13788; and International Patent Application No. WO 93/24641, the entire disclosures of which are incorporated herein by reference. In one embodiment, the miR gene products are expressed from a single recombinant AAV vector comprising the CMV intermediate early promoter.

[0122] In a certain embodiment, a recombinant AAV viral vector of the invention comprises a nucleic acid sequence encoding a miR precursor RNA in operable connection with a polyT termination sequence under the control of a human U6 RNA promoter. As used herein, "in operable connection with a polyT termination sequence" means that the nucleic acid sequences encoding the sense or antisense strands are immediately adjacent to the polyT termination signal in the 5' direction. During transcription of the miR sequences from the vector, the polyT termination signals act to terminate transcription.

[0123] In other embodiments of the treatment methods of the invention, an effective amount of at least one compound that inhibits miR expression can be administered to the subject. As used herein, "inhibiting miR expression" means that the production of the precursor and/or active, mature form of miR gene product after treatment is less than the amount produced prior to treatment. One skilled in the art can readily determine whether miR expression has been inhibited in cells (e.g., cancerous cells, cells exhibiting a myeloproliferative disorder), using, for example, the techniques for determining miR transcript level discussed herein. Inhibition can occur at the level of gene expression (i.e., by inhibiting transcription of a miR gene encoding the miR gene product) or at the level of processing (e.g., by inhibiting processing of a miR precursor into a mature, active miR).

[0124] As used herein, an "effective amount" of a compound that inhibits miR expression is an amount sufficient to inhibit proliferation of cells (e.g., cancerous cells, cells exhibiting a myeloproliferative disorder) in a subject suffering from cancer and/or a myeloproliferative disorder. One skilled in the art can readily determine an effective amount of a miR expression-inhibiting compound to be administered to a given subject, by taking into account factors, such as the size and weight of the subject; the extent of disease penetration; the age, health and sex of the subject; the route of administration; and whether the administration is regional or systemic.

[0125] For example, an effective amount of the expression-inhibiting compound can be based on the approximate weight of a tumor mass to be treated, as described herein. An effective amount of a compound that inhibits miR expression can also be based on the approximate or estimated body weight of a subject to be treated, as described herein.

[0126] One skilled in the art can also readily determine an appropriate dosage regimen for administering a compound that inhibits miR expression to a given subject, as described herein. Suitable compounds for inhibiting miR gene expression include double-stranded RNA (such as short- or small-interfering RNA or "siRNA"), antisense nucleic acids, and enzymatic RNA molecules, such as ribozymes. Each of those compounds can be targeted to a given miR gene product and interfere with the expression (e.g., by inhibiting translation, by inducing cleavage and/or degradation) of the target miR gene product.

[0127] For example, expression of a given miR gene can be inhibited by inducing RNA interference of the miR gene with an isolated double-stranded RNA ("dsRNA") molecule which has at least 90%, for example, at least 95%, at least 98%, at least 99%, or 100%, sequence homology with at least a portion of the miR gene product. In a particular embodiment, the dsRNA molecule is a "short or small interfering RNA" or "siRNA."

[0128] siRNA useful in the present methods comprise short double-stranded RNA from about 17 nucleotides to about 29 nucleotides in length, preferably from about 19 to about 25 nucleotides in length. The siRNA comprise a sense RNA strand and a complementary antisense RNA strand annealed together by standard Watson-Crick base-pairing interactions (hereinafter "base-paired"). The sense strand comprises a nucleic acid sequence that is substantially identical to a nucleic acid sequence contained within the target miR gene product.

[0129] As used herein, a nucleic acid sequence in an siRNA that is "substantially identical" to a target sequence contained within the target mRNA is a nucleic acid sequence that is identical to the target sequence, or that differs from the target sequence by one or two nucleotides. The sense and antisense strands of the siRNA can comprise two complementary, single-stranded RNA molecules, or can comprise a single molecule in which two complementary portions are base-paired and are covalently linked by a single-stranded "hairpin" area.

[0130] The siRNA can also be altered RNA that differs from naturally-occurring RNA by the addition, deletion, substitution and/or alteration of one or more nucleotides. Such alterations can include addition of non-nucleotide material, such as to the end(s) of the siRNA or to one or more internal nucleotides of the siRNA, or modifications that make the siRNA resistant to nuclease digestion, or the substitution of one or more nucleotides in the siRNA with deoxyribonucleotides.

[0131] One or both strands of the siRNA can also comprise a 3' overhang. As used herein, a "3' overhang" refers to at least one unpaired nucleotide extending from the 3'-end of a duplexed RNA strand. Thus, in certain embodiments, the siRNA comprises at least one 3' overhang of from 1 to about 6 nucleotides (which includes ribonucleotides or deoxyribonucleotides) in length, from 1 to about 5 nucleotides in length, from 1 to about 4 nucleotides in length, or from about 2 to about 4 nucleotides in length. In a particular embodiment, the 3' overhang is present on both strands of the siRNA, and is 2 nucleotides in length. For example, each strand of the siRNA can comprise 3' overhangs of dithymidylic acid ("TT") or diuridylic acid ("uu").

[0132] The siRNA can be produced chemically or biologically, or can be expressed from a recombinant plasmid or viral vector, as described above for the isolated miR gene products. Exemplary methods for producing and testing dsRNA or siRNA molecules are described in U.S. Published Patent Application No. 2002/0173478 to Gewirtz and in U.S. Published Patent Application No. 2004/0018176 to Reich et al*.,* the entire disclosures of both of which are incorporated herein by reference.

[0133] Expression of a given miR gene can also be inhibited by an antisense nucleic acid. As used herein, an "antisense nucleic acid" refers to a nucleic acid molecule that binds to target RNA by means ofRNA-RNA, RNA-DNA or RNA-peptide nucleic acid interactions, which alters the activity of the target RNA. Antisense nucleic acids suitable for use in the present methods are single-stranded nucleic acids (e.g., RNA, DNA, RNA-DNA chimeras, peptide nucleic acids (PNA)) that generally comprise a nucleic acid sequence complementary to a contiguous nucleic acid sequence in a miR gene product. The antisense nucleic acid can comprise a nucleic acid sequence that is 50-100% complementary, 75-100% complementary, or 95-100% complementary to a contiguous nucleic acid sequence in a miR gene product. Nucleic acid sequences of particular human miR gene products are provided in Table 1a and Table 1b. Without wishing to be bound by any theory, it is believed that the antisense nucleic acids activate RNase H or another cellular nuclease that digests the miR gene product/antisense nucleic acid duplex.

[0134] Antisense nucleic acids can also contain modifications to the nucleic acid backbone or to the sugar and base moieties (or their equivalent) to enhance target specificity, nuclease resistance, delivery or other properties related to efficacy of the molecule. Such modifications include cholesterol moieties, duplex intercalators, such as acridine, or one or more nuclease-resistant groups.

[0135] Antisense nucleic acids can be produced chemically or biologically, or can be expressed from a recombinant plasmid or viral vector, as described above for the isolated miR gene products. Exemplary methods for producing and testing are within the skill in the art; *see, e.g.,* Stein and Cheng (1993), Science 261:1004 and U.S. Patent No. 5,849,902 to Woolf et al*.,* the entire disclosures of which are incorporated herein by reference.

[0136] Expression of a given miR gene can also be inhibited by an enzymatic nucleic acid. As used herein, an "enzymatic nucleic acid" refers to a nucleic acid comprising a substrate binding region that has complementarity to a contiguous nucleic acid sequence of a miR gene product, and which is able to specifically cleave the miR gene product. The enzymatic nucleic acid substrate binding region can be, for example, 50-100% complementary, 75-100% complementary, or 95-100% complementary to a contiguous nucleic acid sequence in a miR gene product. The enzymatic nucleic acids can also comprise modifications at the base, sugar, and/or phosphate groups. An exemplary enzymatic nucleic acid for use in the present methods is a ribozyme.

[0137] The enzymatic nucleic acids can be produced chemically or biologically, or can be expressed from a recombinant plasmid or viral vector, as described above for the isolated miR gene products. Exemplary methods for producing and testing dsRNA or siRNA molecules are described in Werner and Uhlenbeck (1995), Nucleic Acids Res. 23:2092-96; Hammann et al. (1999), Antisense and Nucleic Acid Drug Dev. 9:25-31; and U.S. Patent No. 4,987,071 to Cech et al*,* the entire disclosures of which are incorporated herein by reference.

[0138] Administration of at least one miR gene product, or at least one compound for inhibiting miR expression, will

inhibit the proliferation of cells (e.g., cancerous cells, cells exhibiting a myeloproliferative disorder) in a subject who has a cancer and/or a myeloproliferative disorder. As used herein, to "inhibit the proliferation of cancerous cells or cells exhibiting a myeloproliferative disorder" means to kill the cells, or permanently or temporarily arrest or slow the growth of the cells. Inhibition of cell proliferation can be inferred if the number of such cells in the subject remains constant or decreases after administration of the miR gene products or miR gene expression-inhibiting compounds. An inhibition of proliferation of cancerous cells or cells exhibiting a myeloproliferative disorder can also be inferred if the absolute number of such cells increases, but the rate of tumor growth decreases.

[0139] The number of cancer cells in the body of a subject can be determined by direct measurement, or by estimation from the size of primary or metastatic tumor masses. For example, the number of cancer cells in a subject can be measured by immunohistological methods, flow cytometry, or other techniques designed to detect characteristic surface markers of cancer cells.

[0140] The size of a tumor mass can be ascertained by direct visual observation, or by diagnostic imaging methods, such as X-ray, magnetic resonance imaging, ultrasound, and scintigraphy. Diagnostic imaging methods used to ascertain size of the tumor mass can be employed with or without contrast agents, as is known in the art. The size of a tumor mass can also be ascertained by physical means, such as palpation of the tissue mass or measurement of the tissue mass with a measuring instrument, such as a caliper.

[0141] The miR gene products or miR gene expression-inhibiting compounds can be administered to a subject by any means suitable for delivering these compounds to cells (e.g., cancer cells, cells exhibiting a myeloproliferative disorder) of the subject. For example, the miR gene products or miR expression-inhibiting compounds can be administered by methods suitable to transfect cells of the subject with these compounds, or with nucleic acids comprising sequences encoding these compounds. In one embodiment, the cells are transfected with a plasmid or viral vector comprising sequences encoding at least one miR gene product or miR gene expression-inhibiting compound.

[0142] Transfection methods for eukaryotic cells are well known in the art, and include, e.g., direct injection of the nucleic acid into the nucleus or pronucleus of a cell; electroporation; liposome transfer or transfer mediated by lipophilic materials; receptor-mediated nucleic acid delivery, bioballistic or particle acceleration; calcium phosphate precipitation, and transfection mediated by viral vectors.

[0143] For example, cells can be transfected with a liposomal transfer compound, e.g., DOTAP (N-[1-(2,3-dioleoyloxy) propyl]-N,N,N-trimethyl-ammonium methylsulfate, Boehringer-Mannheim) or an equivalent, such as LIPOFECTIN. The amount of nucleic acid used is not critical to the practice of the invention; acceptable results may be achieved with 0.1-100 micrograms of nucleic acid/10^5 cells. For example, a ratio of about 0.5 micrograms of plasmid vector in 3 micrograms of DOTAP per 10^5 cells can be used.

[0144] A miR gene product or miR gene expression-inhibiting compound can also be administered to a subject by any suitable enteral or parenteral administration route. Suitable enteral administration routes for the present methods include, e.g., oral, rectal, or intranasal delivery. Suitable parenteral administration routes include, e.g., intravascular administration (e.g., intravenous bolus injection, intravenous infusion, intra-arterial bolus injection, intra-arterial infusion and catheter instillation into the vasculature); peri- and intra-tissue injection (e.g., peri-tumoral and intra-tumoral injection, intra-retinal injection, or subretinal injection); subcutaneous injection or deposition, including subcutaneous infusion (such as by osmotic pumps); direct application to the tissue of interest, for example by a catheter or other placement device (e.g., a retinal pellet or a suppository or an implant comprising a porous, non-porous, or gelatinous material); and inhalation. Particularly suitable administration routes are injection, infusion and direct injection into the tumor.

[0145] In the present methods, a miR gene product or miR gene product expression-inhibiting compound can be administered to the subject either as naked RNA, in combination with a delivery reagent, or as a nucleic acid (e.g., a recombinant plasmid or viral vector) comprising sequences that express the miR gene product or miR gene expression-inhibiting compound. Suitable delivery reagents include, e.g., the Mirus Transit TKO lipophilic reagent; LIPOFECTIN; lipofectamine; cellfectin; polycations (*e.g.*, polylysine) and liposomes.

[0146] Recombinant plasmids and viral vectors comprising sequences that express the miR gene products or miR gene expression-inhibiting compounds, and techniques for delivering such plasmids and vectors to cancer cells, are discussed herein and/or are well known in the art.

[0147] In a particular embodiment, liposomes are used to deliver a miR gene product or miR gene expression-inhibiting compound (or nucleic acids comprising sequences encoding them) to a subject. Liposomes can also increase the blood half-life of the gene products or nucleic acids. Suitable liposomes for use in the invention can be formed from standard vesicle-forming lipids, which generally include neutral or negatively charged phospholipids and a sterol, such as cholesterol. The selection of lipids is generally guided by consideration of factors, such as the desired liposome size and half-life of the liposomes in the blood stream. A variety of methods are known for preparing liposomes, for example, as described in Szoka et al. (1980), Ann. Rev. Biophys. Bioeng. 9:467; and U.S. Patent Nos. 4,235,871, 4,501,728, 4,837,028, and 5,019,369, the entire disclosures of which are incorporated herein by reference.

[0148] The liposomes for use in the present methods can comprise a ligand molecule that targets the liposome to cancer cells. Ligands that bind to receptors prevalent in cancer cells, such as monoclonal antibodies that bind to tumor

cell antigens, are preferred.

[0149] The liposomes for use in the present methods can also be modified so as to avoid clearance by the mononuclear macrophage system ("MMS") and reticuloendothelial system ("RES"). Such modified liposomes have opsonization-inhibition moieties on the surface or incorporated into the liposome structure. In a particularly preferred embodiment, a liposome of the invention can comprise both an opsonization-inhibition moiety and a ligand.

[0150] Opsonization-inhibiting moieties for use in preparing the liposomes of the invention are typically large hydrophilic polymers that are bound to the liposome membrane. As used herein, an opsonization-inhibiting moiety is "bound" to a liposome membrane when it is chemically or physically attached to the membrane, e.g., by the intercalation of a lipid-soluble anchor into the membrane itself, or by binding directly to active groups of membrane lipids. These opsonization-inhibiting hydrophilic polymers form a protective surface layer that significantly decreases the uptake of the liposomes by the MMS and RES; e.g., as described in U.S. Patent No. 4,920,016, the entire disclosure of which is incorporated herein by reference.

[0151] Opsonization-inhibiting moieties suitable for modifying liposomes are preferably water-soluble polymers with a number-average molecular weight from about 500 to about 40,000 daltons, and more preferably from about 2,000 to about 20,000 daltons. Such polymers include polyethylene glycol (PEG) or polypropylene glycol (PPG) or derivatives thereof; e.g., methoxy PEG or PPG, and PEG or PPG stearate; synthetic polymers, such as polyacrylamide or poly N-vinyl pyrrolidone; linear, branched, or dendrimeric polyamidoamines; polyacrylic acids; polyalcohols, e.g., polyvinylalcohol and polyxylitol to which carboxylic or amino groups are chemically linked, as well as gangliosides, such as ganglioside GM1. Copolymers of PEG, methoxy PEG, or methoxy PPG, or derivatives thereof, are also suitable. In addition, the opsonization-inhibiting polymer can be a block copolymer of PEG and either a polyamino acid, polysaccharide, polyamidoamine, polyethyleneamine, or polynucleotide. The opsonization-inhibiting polymers can also be natural polysaccharides containing amino acids or carboxylic acids, e.g., galacturonic acid, glucuronic acid, mannuronic acid, hyaluronic acid, pectic acid, neuraminic acid, alginic acid, carrageenan; aminated polysaccharides or oligosaccharides (linear or branched); or carboxylated polysaccharides or oligosaccharides, e.g., reacted with derivatives of carbonic acids with resultant linking of carboxylic groups. Preferably, the opsanization-inhibiting moiety is a PEG, PPG, or a derivative thereof. Liposomes modified with PEG or PEG-derivatives are sometimes called "PEGylated liposomes."

[0152] The opsonization-inhibiting moiety can be bound to the liposome membrane by any one of numerous well-known techniques. For example, an N-hydroxysuccinimide ester of PEG can be bound to a phosphatidyl-ethanolamine lipid-soluble anchor, and then bound to a membrane. Similarly, a dextran polymer can be derivatized with a stearylamine lipid-soluble anchor via reductive amination using $Na(CN)BH_3$ and a solvent mixture, such as tetrahydrofuran and water in a 30:12 ratio at 60˚C.

[0153] Liposomes modified with opsonization-inhibition moieties remain in the circulation much longer than unmodified liposomes. For this reason, such liposomes are sometimes called "stealth" liposomes. Stealth liposomes are known to accumulate in tissues fed by porous or "leaky" microvasculature. Thus, tissue characterized by such microvasculature defects, for example, solid tumors, will efficiently accumulate these liposomes; see Gabizon, et al. (1988), Proc. Natl. Acad. Sci., U.S.A., 18:6949-53. In addition, the reduced uptake by the RES lowers the toxicity of stealth liposomes by preventing significant accumulation of the liposomes in the liver and spleen. Thus, liposomes that are modified with opsonization-inhibition moieties are particularly suited to deliver the miR gene products or miR gene expression-inhibition compounds (or nucleic acids comprising sequences encoding them) to tumor cells.

[0154] The miR gene products or miR gene expression-inhibition compounds can be formulated as pharmaceutical compositions, sometimes called "medicaments," prior to administering them to a subject, according to techniques known in the art. Accordingly, the invention encompasses pharmaceutical compositions for treating cancer and/or a myeloproliferative disorder.

[0155] In one embodiment, the pharmaceutical composition of the invention comprises at least one miR expression-inhibition compound and a pharmaceutically-acceptable carrier. In a particular embodiment, the at least one miR expression-inhibition compound is specific for a miR gene product whose expression is greater in cancer cells than control cells (i.e., it is upregulated). In another embodiment, the miR expression-inhibition compound is specific for one or more miR gene products selected from the group consisting of miR-101, miR-126, miR-99a, miR-99-prec, miR-106, miR-339, miR-99b, miR-149, miR-33, miR-135 and miR-20. In another embodiment, the miR expression-inhibition compound is specific for one or more miR gene products selected from the group consisting of miR-101, miR-126, miR-106, miR-20, and miR-135. In yet another embodiment, the miR expression-inhibition compound is specific for one or more miR gene products selected from the group consisting of miR-106, miR-20 and miR-135.

[0156] In other embodiments, the pharmaceutical compositions comprise an effective amount of at least one miR gene product, or an isolated variant or biologically-active fragment thereof, and a pharmaeeutioally-acceptable carrier. In one embodiment, the invention is a pharmaceutical composition for treating a cancer and/or a myeloproliferative disorder, wherein the cancer and/or myeloproliferative disorder is associated with overexpression of a MAFB gene product. In this embodiment, the pharmaceutical composition comprises at least one miR gene product that binds to, and decreases expression of, the MAFB gene product. In a particular embodiment, the at least one miR gene product

comprises a nucleotide sequence that is complementary to a nucleotide sequence in the MAFB gene product. In another embodiment, the at least one miR gene product is miR-130a or an isolated variant or biologically-active fragment thereof.

[0157] In one embodiment, the invention is a pharmaceutical composition for treating a cancer and/or a myeloproliferative disorder, wherein the cancer and/or myeloproliferative disorder is associated with overexpression of a HOXA1 gene product. In this embodiment, the pharmaceutical composition comprises at least one miR gene product that binds to, and decreases expression of, the HOXA1 gene product. In a particular embodiment, the at least one miR gene product comprises a nucleotide sequence that is complementary to a nucleotide sequence in the HOX1 gene product. In another embodiment, the at least one miR gene product is miR-10a or an isolated variant or biologically-active fragment thereof.

[0158] Pharmaceutical compositions of the present invention are characterized as being at least sterile and pyrogen-free. As used herein, "pharmaceutical compositions" include formulations for human and veterinary use. Methods for preparing pharmaceutical compositions of the invention are within the skill in the art, for example, as described in Remington's Pharmaceutical Science, 17th ed., Mack Publishing Company, Easton, PA. (1985), the entire disclosure of which is incorporated herein by reference.

[0159] The present pharmaceutical compositions comprise at least one miR gene product or miR gene expression-inhibition compound (or at least one nucleic acid comprising a sequence encoding the miR gene product or miR gene expression-inhibition compound) (e.g., 0.1 to 90% by weight), or a physiologically-acceptable salt thereof, mixed with a pharmaceutically-acceptable carrier. In certain embodiments, the pharmaceutical composition of the invention additionally comprises one or more anti-cancer agents (e.g., chemotherapeutic agents). The pharmaceutical formulations of the invention can also comprise at least one miR gene product or miR gene expression-inhibition compound (or at least one nucleic acid comprising a sequence encoding the miR gene product or miR gene expression-inhibition compound), which are encapsulated by liposomes and a pharmaceutically-acceptable carrier. In one embodiment, the pharmaceutical composition comprises a miR gene or gene product that is not miR-15, miR-16, miR-143 and/or miR-145.

[0160] Especially suitable pharmaceutically-acceptable carriers are water, buffered water, normal saline, 0.4% saline, 0.3% glycine, hyaluronic acid and the like.

[0161] In a particular embodiment, the pharmaceutical compositions of the invention comprise at least one miR gene product or miR gene expression-inhibition compound (or at least one nucleic acid comprising a sequence encoding the miR gene product or miR gene expression-inhibition compound) that is resistant to degradation by nucleases. One skilled in the art can readily synthesize nucleic acids that are nuclease resistant, for example by incorporating one or more ribonucleotides that is modified at the 2'-position into the miR gene product. Suitable 2'-modified ribonucleotides include those modified at the 2'-position with fluoro, amino, alkyl, alkoxy and O-allyl.

[0162] Pharmaceutical compositions of the invention can also comprise conventional pharmaceutical excipients and/or additives. Suitable pharmaceutical excipients include stabilizers, antioxidants, osmolality adjusting agents, buffers, and pH adjusting agents. Suitable additives include, e.g., physiologically biocompatible buffers (e.g., tromethamine hydrochloride), additions of chelants (such as, for example, DTPA or DTPA-bisamide) or calcium chelate complexes (such as, for example, calcium DTPA, CaNaDTPA-bisamide), or, optionally, additions of calcium or sodium salts (for example, calcium chloride, calcium ascorbate, calcium gluconate or calcium lactate). Pharmaceutical compositions of the invention can be packaged for use in liquid form, or can be lyophilized.

[0163] For solid pharmaceutical compositions of the invention, conventional nontoxic solid pharmaceutically-acceptable carriers can be used; for example, pharmaceutical grades of mannitol, lactose, starch, magnesium stearate, sodium saccharin, talcum, cellulose, glucose, sucrose, magnesium carbonate, and the like.

[0164] For example, a solid pharmaceutical composition for oral administration can comprise any of the carriers and excipients listed above and 10-95%, preferably 25%-75%, of the at least one miR gene product or miR gene expression-inhibition compound (or at least one nucleic acid comprising sequences encoding them). A pharmaceutical composition for aerosol (inhalational) administration can comprise 0.01-20% by weight, preferably 1%-10% by weight, of the at least one miR gene product or miR gene expression-inhibition compound (or at least one nucleic acid comprising a sequence encoding the miR gene product or miR gene expression-inhibition compound) encapsulated in a liposome as described above, and a propellant. A carrier can also be included as desired; e.g., lecithin for intranasal delivery.

[0165] The pharmaceutical compositions of the invention can further comprise one or more anti-cancer agents. In a particular embodiment, the compositions comprise at least one miR gene product or miR gene expression-inhibition compound (or at least one nucleic acid comprising a sequence encoding the miR gene product or miR gene expression-inhibition compound) and at least one chemotherapeutic agent. Chemotherapeutic agents that are suitable for the methods of the invention include, but are not limited to, DNA-alkylating agents, antitumor antibiotic agents, anti-metabolic agents, tubulin stabilizing agents, tubulin destabilizing agents, hormone antagonist agents, topoisomerase inhibitors, protein kinase inhibitors, HMG-CoA inhibitors, CDK inhibitors, cyclin inhibitors, caspase inhibitors, metalloproteinase inhibitors, antisense nucleic acids, triple-helix DNAs, nucleic acids aptamers, and molecularly-modified viral, bacterial and exotoxic agents. Examples of suitable agents for the compositions of the present invention include, but are not limited to, cytidine arabinoside, methotrexate, vincristine, etoposide (VP-16), doxorubicin (adriamycin), cisplatin (CDDP),

dexamethasone, arglabin, cyclophosphamide, sarcolysin, methylnitrosourea, fluorouracil, 5-fluorouracil (5FU), vinblastine, camptothecin, actinomycin-D, mitomycin C, hydrogen peroxide, oxaliplatin, irinotecan, topotecan, leucovorin, carmustine, streptozocin, CPT-11, taxol, tamoxifen, dacarbazine, rituximab, daunorubicin, 1-β-D-arabinofuranosylaytosine, imatinib, fludarabine, docetaxel and FOLFOX4.

[0166] The invention also encompasses methods of identifying an anti-cancer agent, comprising providing a test agent to a cell and measuring the level of at least one miR gene product in the cell. In one embodiment, the method comprises providing a test agent to a cell and measuring the level of at least one miR gene product associated with increased expression levels in cancer cells (e.g., in AMKL eells). A decrease in the level of the miR gene product that is associated with increased expression levels in cancer, relative to a suitable control (e.g., the level of the miR gene product in control cells), is indicative of the test agent being an anti-cancer agent. In a particular embodiment, the at least one miR gene product associated with increased expression levels in cancer cells is selected from the group consisting of miR-101, miR-126, miR-99a, miR-99-prec, miR-106, miR-339, miR-99b, miR-149, miR-33, miR-135 and miR-20. In another embodiment, the at least one miR gene product associated with increased expression levels in cancer cells is selected from the group consisting of miR-101, miR-126, miR-106, miR-20 and miR-135. In yet another embodiment, the at least one miR gene product associated with increased expression levels in cancer cells is selected from the group consisting of miR-106, miR-20 and miR-135. In one embodiment, the miR gene product is not one or more of let7a-2, let-7c, let-7g, let-7i, miR-7-2, miR-7-3, miR-9, miR-9-1, miR-10a, miR-15a, miR-15b, miR-16-1, miR-16-2, miR-17-5p, miR-20a, miR-21, miR-24-1, miR-24-2, miR-25, miR-29b-2, miR-30, miR-30a-5p, miR-30c, miR-30d, miR-31, miR-32, miR-34, miR-34a, miR-34a prec, miR-34a-1, miR-34a-2, miR-92-2, miR-96, miR-99a, miR-99b prec, miR-100, miR-103, miR-106a, miR-107, miR-123, miR-124a-1, miR-125b-1, miR-125b-2, miR-126*, miR-127, miR-128b, miR-129, miR-129-1/2 prec, miR-132, miR-135-1, miR-136, miR-137, miR-141, miR-142-as, miR-143, miR-146, miR-148, miR-149, miR-153, miR-155, miR 159-1, miR-181, miR-181b-1, miR-182, miR-196, miR-191, miR-192, miR-195, miR-196-1, miR-196-1 prec, miR-196-2, miR-199a-1, miR-199a-2, miR-199b, miR-200b, miR-202, rniR-203, miR-204, miR-205, miR-210, miR-211, miR-212, miR-214, miR-215, nniR-217, miR-221 and/or miR-223.

[0167] In one embodiment, the method comprises providing a test agent to a cell and measuring the level of at least one miR gene product associated with decreased expression levels in cancerous cells. An increase in the level of the miR gene product in the cell, relative to a to a suitable control (e.g., the level of the miR gene product in a control cell), is indicative of the test agent being an anti-cancer agent.

[0168] Suitable agents include, but are not limited to drugs (e.g., small molecules, peptides), and biological macromolecules (e.g., proteins, nucleic acids). The agent can be produced recombinantly, synthetically, or it may be isolated (i.e., purified) from a natural source. Various methods for providing such agents to a cell (e.g., transfection) are well known in the art, and several of such methods are described hereinabove. Methods for detecting the expression of at least one miR gene product (e.g., Northern blotting, *in situ* hybridization, RT-PCR, expression profiling) are also well known in the art. Several of these methods are also described herein.

[0169] The invention will now be illustrated by the following non-limiting examples.

[0170] EXEMPLIFICATION

[0171] Unless otherwise noted, the following materials and methods were used in the Examples.

[0172] Material and methods

[0173] Cell Lines and Human $CD34^+$ Cells

[0174] The human chronic myeloid leukemia (CML) blast crisis cell lines K-562 and MEG-01 were obtained from American Type Tissue Culture (ATCC, Manassas, VA) and maintained in RPMI 1640 (GIBCO, Carlsbad, CA) containing 10% FBS with penicillin-gentamycin at 37˚C with 5% CO2. The human megakaryoblastic leukemia cells UT-7, and CMK, and the chronic myeloid leukemia (CML) in blast crisis LAMA were obtained from DSMZ (Braunsweig, Germany). All cells were maintained in RPMI medium 1640 with 20% FBS and antibiotics, except UT-7 which is factor-dependent and was cultured in MEM-α with 20% FBS and 5 ng/ml GM-CSF. Fresh and frozen human bone marrow $CD34^+$ cells were obtained from Stemcell Technologies (Vancouver, B.C., Canada). FACS analysis for CD34 antigen revealed a purity >98%.

[0175] *Human Progenitor $CD34^+$ Cell Cultures.*

[0176] Human bone marrow $CD34^+$ cells were grown in STEM-media (Stemcell Technologies), which includes Isocove modified Dulbecco's medium supplemented with human transferrin, insulin, bovine serine albumin, human low density lipoprotein and glutamine, in the presence of 100 ng/ml human recombinant thrombopoietin (TPO) for the first 4 days, followed by a combination of 100 ng/ml TPO, IL3, and SCF (cytokine mixture CC-200, Stemcell Technologies). The initial cell density was 100,000 cells/ml; three times a week, the cell density was adjusted to 100,000 to 200,000 cells/ml. To increase the purity of the cells for microarray analysis, cell sorting was performed at day 10 of culture. Cells were incubated on ice for 45 minutes with anti-human $CD34^+$, anti-human $CD41^+$, anti-human $CD61^+$, and their respective isotypes. After washing twice with PBS 3% FBS, cells were sorted using a FACS Aria sorting machine in bulk in two separate populations; $CD34^-$ $CD61^+$ and $CD34^+$ $CD61^+$ cells for culture and RNA extraction. The purity of the sorted populations was greater than 95%.

[0177] *Megakaryocytes Characterization.*

[0178] Cytospin preparations of $CD34^+$ progenitors in culture were performed and stained with May-Grunwald Giemsa at different time points during the megakaryocytic differentiation induction. For FACS analysis, the primary antibodies that were used were as follows: CD41A, CD61A, CD42B, and CD34 with their respective isotypes (BD Pharmingen, San Diego, CA). Cytometric studies were performed as previously described (Tajima, S., et al. (1996) J. Exp. Med 184,1357-1364) using a FACScalibur (BD Biosciences) and the CELLQUEST software (BD Biosciences).

[0179] *RNA Extraction, Northern Blotting and miRNA Microarray Experiments.*

[0180] Procedures were performed as described in detail elsewhere (Liu, C.G., et al. (2002) Proc. Natl. Acad. Sci. USA 101, 9740-9744). Raw data were normalized and analyzed in GENESPRING 7.2 software (zoomSilicon Genetics, Redwood City, CA). Expression data were median-centered by using both GENESPRING normalization option and global median normalization of the BIOCONDUCTOR package (www.bioconductor.org) with similar results. Statistical comparisons were done by using the GENBSPRING ANOVA tool, predictive analysis of microarray (PAM) and the significance analysis of microarray (SAM) software (www-stat.stanford.edu/~tibs/SAM/index.html).

[0181] *Reverse Transcriptase PCR (RT-PCR) and Real Time PCR.*

[0182] Total RNA isolated with Trizol reagent (Invitrogen, Carlsbad, CA) was processed after DNAase treatment (Ambion, Austin, TX) directly to cDNA by reverse transcription using Superscript II (Invitrogen). Comparative real-time PCR was performed in triplicate. Primers and probes were obtained from Applied Biosystems (Foster City, CA) for the following genes: HOXA1, HOXA3, HOXB4, HOXB5, and HOXD10. Gene expression levels were quantified by using the ABI Prism 7900 Sequence detection system (Applied Biosystems). Normalization was performed by using the 18S RNA primer kit. Relative expression was calculated by using the computed tomography (CT) method. RT-PCR also was performed by using the following oligonucleotide primers:

[0183] MAFB FW; 5'-AACTTTGTCTTGGGGGACAC-3'(SEQ ID NO:499);

[0184] MAFB RW; 5'-GAGGGGAGGATCTGTTTTCC-3' (SEQ ID NO:500);

[0185] HOXA1 FW; 5'-CCAGGAGCTCAGGAAGAAGA GAT-3' (SEQ ID NO:501); and

[0186] HOXA1 RW; S'-CCCTCTGAGGCATCTGATTGGGTTT-3' (SEQ ID NO:502).

[0187] *Real-Time Quantification of miRNAs by Stem-Loop RT-PCR.*

[0188] Real time-PCR for pri-miRNAs 10a, miR15a, miR16-1, miR-130a, miR-20, miR-106, miR-17-5, miR-181b, miR-99a, and miR-126 were performed as described (Chen, C., et al. (2005) Nucl. Acid's Res. 33, e179. 18S was used for normalization. All reagents and primers were obtained from Applied Biosystems.

[0189] *Bioinformatics.*

[0190] miRNA target prediction of the differentially expressed miRNAs was performed by using TARGETSCAN (www.genes.mit.edu/targetsean), MIRANDA (www.mskc.miranda.org), and PICTAR (www.pictar.bio.nyu.edu) software.

[0191] *Cell Transfection with miRNA Precursors.*

[0192] miRNA precursors *miR-10a* and *miR-130a* were purchased from Ambion: Five million K562 cells were nucleoporated by using Amaxa (Gaithesburg, MD) with 5 μg of precursor oligonucleotides in a total volume of 10 ml. The expression of the oligonucleotides was assessed by Northern blots and RT-PCR as described.

[0193] *Luciferase Reporter Experiments.*

[0194] The 3' UTR segments containing the target sites for *miR-10a* and *miR-130a* from *HOXA1* and *MAFB* genes, respectively, were amplified by PCR from genomic DNA and inserted into the pGL3 control vector (Promega, Madison, WI), by using the XbaI site immediately downstream from the stop codon of luciferase. The following oligonucleotide primer sets were used to generate specific fragments:

[0195] MAFB FW 5'-GCATCTAGAGCACCCCAGAGGAGTGT-3' (SEQ ID NO:503);

[0196] MAFB RW 5'-GCATCTAGACAAGCACCATGCGGTTC-3' (SEQ ID NO:504);

[0197] HOXA1 FW 5'-TACTCTAGACCAGGAGCTCAGGAAGA-3' (SEQ ID NO:505); and

[0198] ROXA1 RW 5'-MCATTCTAGATGAGGCATCTGATTGGG-3' (SEQ ID NO:506).

[0199] We also generated two inserts with deletions of 5 bp and 9 bp, respectively, from the site of perfect complementarity by using the QuikChange XL-site directed Mutagenesis Kit (Stratagene, La Jolla, CA). Wild type (WT) and mutant insert were confirmed by sequencing,

[0200] Human chronic myeloid leukemia (CML) in megakaryoblastic crisis cell line (MEG-01) was cotransfected in six-well plates by using Lipofectamine 2000 (Invitrogen) according to the manufacturer's protocol with 0.4 μg of the firefly luciferase report vector and 0.08 μg of the control vector containing Renilla luciferase, pRL-TK (Promega). For each well, 10 nM of the premiR-130a and premiR-10a precursors (Ambion) were used. Firefly and Renilla luciferase activities were measured consecutively by using the dual luciferase assays (Promega) 24 hours after transfection.

[0201] *Western Blots.*

[0202] Total and nuclear protein extracts from K562 cells transfected with miR-10a and miR-130a, as well as $CD34^+$ cells at different stages of megakaryocytic differentiation were extracted by using RIPA buffer or Nuclear extraction Kit (Pierce, Rockford, IL). Protein expression was analyzed by Western blotting with the following primary antibodies: MAFB (Santa Cruz Biotechnology, Santa Cruz, CA), HOXA1 (R&D Systems, Minneapolis, MN), β-Actin and Nucleolin (Santa

Cruz Biotechnology). Appropriate secondary antibodies were used (Santa Cruz Biotechnology).

[0203] **Example 1: miRNA Expression During in Vitro Megakaryocytic Differentiation of CD34± Progenitors.**

[0204] Using a combination of a specific megakaryocytic growth factor (thrombopoietin) and nonspecific cytokines (SCF and IL-3), we were able to generate *in vitro* pure, abundant megakaryocyte progeny from $CD34^+$ bone marrow progenitors suitable for microarray studies (FIG. 4). Total RNA was obtained for miRNA chip analysis from three different CD34 progenitors at baseline and at days 10, 12, 14 and 16 of culture with cytokines. We initially compared the expression of miRNA between the $CD34^+$ progenitors and the pooled $CD34^+$ differentiated megakaryocytes at all points during the differentiation process. 17 miRNA (Table 1) that are sharply down regulated during megakaryocytic differentiation were identified. There were no statistically significant miRNAs upregulated during megakaryocytic differentiation. Using predictive analysis of microarray (PAM), we identified 8 microRNAs that predicted megakaryocytic differentiation with no misclassification error: miR-10a, miR-10b, miR-30c, miR-106, miR-126, miR-130a, miR-132, and miR-143. All of these miRNAs, except miR-143, are included in the 17 miRNAs identified by significance analysis of microarray (SAM). Northern blots and real-time PCR for several miRNAs confirmed the results obtained by miRNA chip analysis (FIG. 1).

[0205] Because we found mainly downregulation of miRNAs during megakaryocytopoiesis, we hypothesized that these miRNAs may unblock target genes involved in differentiation. In line with this hypothesis, miRNAs that are sharply downregulated in our system are predicted to target genes with important roles in megakaryocytic differentiation. Among the transcription factors with well-known function in megakaryocytopoiesis, RUNX-1 (Elagib, K.E., et al. (2003) Blood, 101:4333-4341), Fli-1 (Athanasoiu, M., et al. (1996) Cell Growth Differ. 7, 1525-1534), FLT1 (Casella, I., et al. (2003) Blood 101, 1316-1323), ETV6 (Hock, H., et al. (2004) Genes Dev. 18:2336-2341), TALI (Begley, C.G., and Green, A.R. (1999) Blood, 93:2760-2770), ETS1 (Jackers, P., et al. (2004) J. Biol. Chem. 279:52183-52190) and CRK (Lannutti, B.J., et al. (2003) Exp. Hematol. 12:1268-1274) are putative targets for several miRNAs downregulated in differentiated megakaryocytes. Moreover, each of these transcription factors has more than one miRNA predicted to be its regulator. For example, RUNX1 (AML1) is predicted to be the target of miR-106, miR-181b, miR-101, let7d and the miR-17-92 cluster. The multiplicity ofmiRNAs predicted to target *AML1* suggests a combinatorial model of regulation.

[0206] We then looked at the temporal expression of miRNAs during the megakaryocytic differentiation process from $CD34^+$ progenitors. We focused on miRNAs that have been described in hematopoietic tissues, such as miR-223, miR-181, miR-155, miR-142, miR-15a, miR-16, miR-106 and the cluster of miR-17-92 (FIG. 5). We found sequential changes in the expression of miR-223. Initially, miR-223 is downregulated during megakaryocytic differentiation, but after 14 days in culture, its expression returns to levels comparable with that of C1734 progenitors (FIG. 1C). The miR-15a and miR-16-1 cluster also follows the same pattern of expression as miR-223 (FIG. 1D), whereas miR-181b, miR-155, miR-106a, miR-17, and miR-20 were downregulated during differentiation (FIG. 6). The temporal variation of the expression of miR-223 and miR-15a/mir-16-1 suggests a stage-specific function.

[0207]

Table 2. miRNAs downregulated during *in vitro* $CD34^+$ megakaryocytic differentiation. All differentially expressed miRNAs have q value <0.01 (false-positive rate).

TABLE 2 **miRNA**	**Chromosomal Location**	**T-test (†)**	**Fold Change**	**Putative targets**
*hsa-mir-010a**	17 q21	-9.10	50.00	*HOXA1, HOXA3, .HOXD10, 50.OOCRK, FLT1*
*hsa-mir-126**	9q34	-2.73	8.33	*CRK, EV12, HOXA9, MAFB, CMAF*
*hsa-mir-106**	xq26.2	-2.63	2.86	*TAL1, FLT1, SKI, RUNX1, FOG2, FL1, PDGFRA, CRK*
*hsa-mir-010b**	2q31	-2.17	11.11	*HOXA1, HOXA3, HOXD10, ETS-1, CRK FLT1*
*hsa-mir-130a**	11q12	-2.08	4.76	*MAFB, MYB, FOG2, CBFB, PDGFRA, SDFR1, CXCL12*
*hsa-mir-130a-prec**	11q12	-2.07	7.69	*NA.*±
hsa-mir-124a	8q23	-1.81	2.78	*TAL1, SK1, FLT1, FOG2, ETS-1, CBFB, RAF1, MYB*

(continued)

TABLE 2 miRNA	Chromosomal Location	T-test (†)	Fold Change	Putative targets
hsa-mir-032-prec	9q31	-1.76	3.57	*NA±*
hsa-mir-101	Ip31.3	-1.75	3.33	*TAL1, CXCL12, MEIS1 ,MEIS2, ETS-1 RUNX1, MYB*
hsa-mir-30c	6q13	-1.71	2.56	*CBFB, MAFG, HOXA1, SBF1, NCOR2, ERG*
*hsa-mir-213**	1q31.3	-1.69	2.38	*MAX-SATB2*
hsa-mir-132-prec	17p13	-1.67	4.17	*NA±*
*hsa-mir-150**	19q13.3	-1.63	5.26	*MYB, SDFR1 TAL1, SKI, RUNX-1,FLT1, CRK, FOG2, RARB*
hsa-mir-020	13q31	-1.62	2.17	*SK1, ETV6, GATA2, FLT1, RAP1B, JUNB, MEIS2 HOXA1,*
hsa-mir-339	7p22	-1.60	3.03	*HOXA9, MEIS2, ITGB3, PLDN HOXA1, HOXD1,*
hsa-let-7a	9q22	-1.58	2.94	*ITGB3, RUNX1, PDGFRA RUNX-1, KIT,*
hsa-let-7d	9q22	-1.56	2.17	*HOXA1, MEIS2, ETS-1 ETV6, PDGFRA RUNX-1, KIT, ITGA3 ,*
hsa-mir-181c	19p13	-1.55	2.50	*HOXA1, MEIS2 ,ETS-1, SDFR1, TAL1, SK1,*
hsa-mir-181b	1q31.3	-1.53	2.13	*FLT1, RUNX1, CRK, FOG1, ETS-*
hsa-mir-017	13q31	-1.38	1.82	*1,MEIS1*

† t test $p<0.05$.

* These miRNAs were identified by PAM as predictors of a megakaryocytic class with the lowest misclassification error. All, except miR-143 are downregulated during megakaryocytic differentiation.

[0208] *NA±:* miRNA precursor sequence that does not contain the mature miRNA, therefore no putative target is shown.

[0209] **Example 2: MAFB Transcription Factor is a Target of *miR-130a.***

[0210] By using three target prediction algorithms (TARGETSCAN (www.genes.mit.edu/targetscan), MIRANDA (www.microma.org/miranda_new.html), and PICTAR (www.piotar.bio.nyu.edu)), we identified that miR-130a is predicted to target MAFB, a transcription factor that is upregulated during megakaryocytic differentiation and induces the GPIIb gene, in synergy with GATE1, SP1 and ETS-1 (Sevinsky, J.R., et al. (2004) Mol. Cell. Biol. 24, 4534-4545). To investigate this putative interaction, first, we examined MAFB protein and mRNA levels in $CD34^+$ progenitors at baseline and after cytokine stimulation (FIG. 2A). We found that the MAFB protein is upregulated during *in vitro* megakaryocytic differentiation. Although the mRNA levels for MAFB by PCR increase with differentiation, this increase does not correlate well with the intensity of its protein expression. The inverse pattern of expression of MAFB and miR-130a suggested *in vivo* interaction that was further investigated.

[0211] To demonstrate a direct interaction between the 3' UTRs of MAFB with miR-130a, we inserted the 3' UTR regions predicted to interact with this miRNA into a luciferase vector. This experiment revealed a repression of about -60% of luciferase activity compared with control vector (FIG. 2B). As an additional control experiment, we used a mutated target mRNA sequence for MAFB lacking five of the complementary bases. As expected, the mutations com-

pletely abolished the interaction between miR-130a and its target 3'UTRs (FIG. 2B).

[0212] We also determined the *in vivo* consequences of overexpressing miR-130a on MAFB expression. The pre-miR-130a and a negative control were transfected by electroporation into K562 cells, which naturally express MAFB and lack miR-130a. Transfection of the pre-miR-130a, but not the control, resulted in a decrease in the protein levels at 48 hours (FIG. 2C). Northern blotting confirmed successful ectopic expression of miR-130a in K562 cells (FIG. 7).

[0213] **Example 3: MiR-10a Correlates with HOXB Gene Expression.**

[0214] It has been reported that in mouse embryos, miR-10a, miR-10b, and miR-196 are expressed in HOX-like patterns (Mansfield, J.H., et al. (2004) Nature 36, 1079-1083) and closely follow their "host" HOX cluster during evolution (Tanzer, A., et al. (2005) J. Exp. Zool. B Mol. Dev. Evol. 304B, 75-85). These data suggest common regulatory elements across paralog clusters. MiR-10a is located at chromosome 17q21 within the cluster of the HOXB genes (FIG. 8) and miR-10b is located at chromosome 2q31 within the HOXD gene cluster. To determine whether the miR-10a expression pattern correlates with the expression of HOXB genes, we performed RT-PCR for HOXB4 and HOXB5, which are the genes located 5' and 3', respectively, to miR-10a in the HOXB cluster. As shown in FIG. 8, HOXB4 and HOXB5 expression paralleled that of miR-10a, suggesting a common regulatory mechanism.

[0215] **Example 4: MiR-10a Downregulates HOXA1.**

[0216] We determined by miRNA array and Northern blot that miR-10a is sharply downregulated during megakaryocytic differentiation. Interestingly, we found several HOX genes as putative targets for miR-10a (Table 2). We thus investigated whether miR-10a could target a HOX gene. We performed real-time PCR for the predicted HOX targets of miR-10: HOXA1, HOXA3, and HOXD10. After normalization with 18S RNA, we found that HOXA1 mRNA is upregulated 7-fold during megakaryocytic differentiation compared with CD34 progenitors (FIG. 3A; see also FIG. 9). HOXA1 protein levels were also upregulated during megakaryocytic differentiation (FIG. 3B). These results are in sharp contrast with the downregulation of miR-10a in megakaryocytic differentiation, suggesting that miR-10a could be an inhibitor of HOXA1 expression. To demonstrate a direct interaction of miR-10a and the 3' UTR sequences of the HOXA1 gene, we carried out a luciferase reporter assay as described in *Material and Methods.* When the miRNA precursor miR-10a was introduced in the MEG01 cells along with the reporter plasmid containing the 3' UTR sequence of *HOXA1,* a 50 % reduction in luciferase activity was observed (FIG. 3C). The degree of complementarity between miR-10a and the HOXA1 3' UTR is shown in Fig. 3D, as predicted by PICTAR (www.pictar.bio.nyu.edu).

[0217] To confirm *in vivo* these findings, we transfected K562 cells with the pre-miR-10a precursor using nucleoporation and measured HOXA1 mRNA expression by RT-PCR and HOXA1 protein levels by Western blotting. Successful ectopic expression of miR-10a was documented by Northern Blot (FIG. 3E). A significant reduction at the mRNA and protein levels for HOXA1 was found for K562 cells transfected with the miR-10a precursor but not with the negative control (FIGS. 3F and 3G). These data indicate that miR-10a targets HOXA1 *in vitro* and *in vivo.*

[0218] It has been reported that miR-196 induces cleavage of HOXBB mRNA, pointing to a posttranscriptional restriction mechanism of HOX gene expression (Yekta, S., et al. (2004) Science, 304:594-596). Contrary to the miR-196-HOXBB interaction, where an almost perfect complementarity exists, the degree of pairing between miR-10a and the human HOXA1 3' UTR is suboptimal (FIG. 4). Although our results indicated target mRNA degradation, further studies are needed to determine whether cleavage or translational repression is the primary mechanism of downregulation of the HOXA1 gene in this system. A previous study using microarray analysis showed that a large number of target mRNA genes are downregulated by miRNA at the level of transcription (Lim, L.P., et al. (2005) Nature: 433,769-771). These data raise the question whether target degradation is a consequence of translational repression and subsequent relocalization of the miR-target complexes to cytoplasmic processing bodies or is a primary event (Pillai, R. (2005) RNA 11, 1753-1761).

[0219] **Example 5: miRNA Profiling in Acute Megakaryoblastic Leukemia (AMKL) Cell Lines.**

[0220] After the identification of the microRNA expression profile of $CD34^+$ cells during megakaryocytic differentiation, we then investigated miRNA expression in AMKL cell lines with the goal to identify differentially expressed miRNAs that could have a pathogenic role in megakaryoblastic leukemia. We initially compared miRNA expression in four AMKL cell lines with that of *in vitro* $CD34^+$-differentiated megakaryocytes. Using significance analysis of microarray (SAM), we identified 10 miRNAs upregulated in AMKL cell lines compared with that of CD34 *in vitro*-differentiated megakaryocytes (Table 3; see also Table 4). These miRNAs are as follows (in order of the fold increase with respect to differentiated megakaryocytes): miR-101, miR-126, miR-99a, miR-99-prec, miR-106, miR-339, miR-99b, miR-149, miR-33 and miR-135. Results were validated by RT-PCR as shown in FIG. 10. Using PAM, we compared miRNA expression in $CD34^+$ cells with *in vitro*-differentiated megakaryocytes and AMKL cell lines (FIG. 10). Interestingly, we found five miRNAs involved in the megakaryocytic differentiation signature (miR-101, miR-126, miR-106, miR-20, and miR-135) that were upregulated in the leukemic cell lines (Tables 3, 5 and 6). Whether this profile represents merely a differentiation state of the cells or has a truly pathogenic role remains to be elucidated. Supporting the second hypothesis, miR-106, miR-135, and miR-20 are predicted to target RUNX1, which is one of the genes most commonly associated with leukemia (Nakao, M., et al, (2004) Oncogene 125, 709-719). Moreover, mutations of RUNX1 have been described in familial thrombocytopenias with a propensity to develop acute myeloid leukemia (Song, W.J., et al. (1999) Nat. Genet.

23,166-175).

[0221] Table 3. microRNAs upregulated in acute megakaryoblastic cell lines compared with *in vitro*-differentiated megakaryocytes

[0222] All the miRNAs have a q value <0.01 (false discovery rate).

[0223] The same miRNAs, except miR-339 and miR-149, were found by using PAM to predict a megakaryoblastic leukemia class with no misclassification error.\

[0224] The results described herein demonstrate that there is a downregulation of miRNAs

TABLE 3

microRNA	Chromosomal Location	*t* test Score	Fold Change	Putative Targets
hsa-mir-101	1p31.3	6.14	11.85	*MEIS2, RUNX1, ETS-1, C-MYB, FOS, RARB, NFE2L2*
hsa-mir-126	9q34	4.91	11.97	*V-CRK*
hsa-mir-099a	21q21	3.30	6.83	*HOXA1, EIF2C, FOXA1*
hsa-mir-099b-prec	21q21	2.85	7.59	*NA*
hsa-mir-106	xq26.2	2.79	3.33	*FLT1, SK1 E2F1, NCDA3, PDGFRA, CRK*
hsa-mir-339	7p22	2.58	3.36	*HOXA1, FLT1, PTP4A1, RAP1B*
hsa-mir-099b	19q13	2.46	4.19	*HOXA1, MYCBP2*
hsa-mir-149	2q37	2.29	3.53	*RAPIA, MAFF, PDGFRA, SP1, NFIB*
hsa-mir-033	2q13	2.27	3.23	*PDGFRA, HIF1A, MEIS2 SP1,HIFIA, SP3, HNRPA1,*
hsa-mir-135	3p21	2.12	3.97	*HOXA10, RUNX1*

during megakaryocytopoiesis. Hypothetically, the downregulation of miRNAs unblocks target genes involved in differentiation. In line with this hypothesis, miRNA that are sharply downregulated in our system are predicted to target genes with important roles in megakaryocytic differentiation. Thus, we have shown that miR-130a targets MAFB, and miR-10a modulates HOXA1. The fact that we found several differentially expressed miR-NAs during differentiation and leukemia that are predicted to target HOXA1 suggests a function for HOXA1 in megakaryocytopoiesis. Loss and gain studies will ultimately be needed to define the role of HOXA1 in this differentiation process. Our findings delineate the expression of miRNAs in megakaryocytic differentiation and suggest a role for miRNA modulation of this lineage by targeting megakaryocytic transcription factors. Furthermore, in megakaryoblastic leukemia cell lines, we have found inverse expression of miRNAs involved in normal megakaryocytic differentiation. These data provide a starting point for future studies of miRNAs in megakaryocytopoiesis and leukemia.

[0225] Table 4. Signature of megakaryocytic differentiation.

TABLE 4

microRNA	CD34 Expression	Megakaryocytic Expression
hsa-mir-010a	up	Down
hsa-mir-126	up	Down
hsa-mir-130a-prec	up	Down
hsa-mir-010b	up	Down
hsa-mir-106	up	Down
hsa-mir-130a	up	Down
hsa-mir-132	up	Down
hsa-mir-30c	up	Down
hsa-mir-143-prec	Down	up

[0226] PAM selected microRNAs with a very low misclassification error.

[0227] Table 5 Signature of megakaryoblastic leukemia cell lines

TABLE 5 MicroRNA	t test Score	Fold Change	Level of Expression in AML M7	Putative Targets
hsa-mir-101-	6.14	11.85	up	*MEIS2, RUNX1, C-MYB, FOS, RARb, NFE2L2*
hsa-mir-126	4.91	11.97	up	*V-CRK*
hsa-mir-099a	3.30	6.83	up	*HOXA1, EIF2C, FOXA1*
hsa-mir-095			up	*SHOX2*
hsa-mir-033	2.27	3.23	up	*PDGFRA, HIFIA, MEIS2*
hsa-mir-135	2.12	3.97	up	*SP1, HIF1A, SP3, HNRPA1, HOXA10, RUNX1*
hsa-mir-099b	2.85	7.59	up	*HOXA1, MYCBP2*
hsa-mir-339	2.58	3.36	up	*HOXA1, FLT1, PTP4A1, RAP1B*
hsa-mir-106	2.79	3.33	up	*HOXA1, EIF2C, FOXA1*
hsa-mir-124a	2.07	2.78	up	*SDFRI,RXRa*
hsa-mir-155			down	*ETS-* 1
hsa-mir-020	2.00	3.09	up	*TAL1, SKI, RUNX-1, FLTI, CRK, FOG2, RARB*
hsa-mir-025	1.98	4.24	up	*GATA2,*
hsa-mir-140			down	*GATA1*

[0228] PAM selected microRNAs. The fold change of miRNA expression is shown alongside *t* test score (SAM) and putative targets.

[0229] Table 6 Three class analysis showing the different regulated microRNAs among the three cell types: $CD34^+$ progenitors, acute megakaryoblastic leukemia cell lines

TABLE 6 microRNA	Chromosomal Location	$CD34^+$ Score	AML M7 cell lines score	*In Vitro*-differentiated Megakaryocytes Score
hsa-mir-010a	17q21	1.0198	0	-0.3562
hsa-mir-101	1p31.3	0	0.814	-0.432
hsa-mir-126	9q34	0.0621	0.4882	-0.4514
hsa-mir-099a	21q21	0	0.4685	-0.2875
hsa-mir-033	22q13	0	0.4258	-0.2294
hsa-mir-095	4p16	0	0.41.42	-0.3567
hsa-mir-010b	2q31	0.3308	0	0
hsa-mir-155	21q21	0	-0.3217	0
hsa-mir-130a	11q12	0.2755	0	0
hsa-let-7d	9q22	0.263	-0.274	0
hsa-mir-099b-pree	21q21	0	0.266	-0.1078
hsa-mir-135-2-prec	12q23	0	0.2279	-0.2566
hsa-mir-339	7p22	0	0.2456	-0.1176
hsa-mir-099b	19q13	0	0.2275	-0.1025
hsa-mir-106	xq26	0	0.0575	-0.1891
hsa-let-7c	21q21	0.0289	-0.1753	0
hsa-mir-148	7p15	0	-0.1748	0
hsa-mir-132-prec	17p13	0.1721	0	0
hsa-mir-020	13q31	0	0.0374	-0.1509

(AMKL) and in vitro-differentiated megakaryocytes.

[0230] There are three patterns of miRNA expression among the three different cell types. The first pattern is defined by miRNA highly expressed in $CD34^+$ cells and downregulated in AMKL and differentiated megakaryocytes. miR-10a

and miR-130a follow this pattern of expression; however, miR-10a is upregulated in AMKL relative to differentiated megakaryocytes. The second pattern is miRNA that is upregulated in AMKL, downregulated in $CD34^+$ cells and differentiated megakaryocytes and includes the following miRNAs: miR-126, miR-99, miR-101, let 7A, and miR-100. The last two miRNAs are equally expressed in $CD34^+$ and differentiated megakaryocytes, rather than showing a gradual decline in expression, as evidenced by miR-126, miR-99 and miR-101. The last pattern includes miRNA-106 and miRNA-135-2, which are upregulated in $CD34^+$ cells and AMKL, but low in differentiated megakaryocytes.

[0231] MicroRNAs are a highly conserved class of non-coding RNAs with important regulatory functions in proliferation, apoptosis, development and differentiation. As described herein, to discover novel regulatory pathways during megakaryocytic differentiation, we performed microRNAs expression profiling of *in vitro*-differentiated megakaryocytes derived from $CD34^+$ hematopoietic progenitors. One major finding was downregulation of miR-10a, miR-126, miR-106, miR-10b, miR-17 and miR-20. Without wishing to be bound to any theory, it is believed that the downregulation of microRNAs unblocks target genes involved in differentiation. It was confirmed in vitro and in vivo that miR-130a targets the transcription factor MAFB, which is involved in the activation of the GPIIB promoter, a key protein for platelet physiology. In addition, it was shown that miR-10a expression in differentiated megakaryocytes is inverse to that of HOXA1, and HOXA1 is a direct target of miR-10a. Finally, the microRNA expression of megakaryoblastic leukemic cell lines was compared to that of in vftro-differentiated megakaryocytes and CD34<+> progenitors. This analysis revealed upregulation of miR-101, miR-126, miR-99a, miR-135, and miR-20 in the cancerous cell line. The data and results described herein delineate the expression of microRNAs during megakaryocytopoiesis and demonstrate a regulatory role of microRNAs in this process by targeting megakaryocytic transcription factors.

The relevant teachings of all publications cited herein that have not explicitly been incorporated by reference, are incorporated herein by reference in their entirety. While this invention has been particularly shown and described with references to preferred embodiments thereof, it will be understood by those skilled in the art that various changes in form and details may be made therein without departing from the scope of the invention encompassed by the appended claims.

While the invention has been described with reference to various and preferred embodiments, it should be understood by those skilled in the art that various changes may be made and equivalents may be substituted for elements thereof without departing from the essential scope of the invention. In addition, many modifications may be made to adapt a particular situation or material to the teachings of the invention without departing from the essential scope thereof. Therefore, it is intended that the invention not be limited to the particular embodiment disclosed herein contemplated for carrying out this invention, but that the invention will include all embodiments falling within the scope of the claims.

The claims of the parent application are given in the Appendix. These are included as part of the description and are included for completeness to preserve all subject matter.

APPENDIX

1. A method of diagnosing or prognosticating cancer and/or a myeloproliferative disorder in a subject, comprising: i) determining the level of at least one miR gene product in a sample from the subject; and ii) comparing the level of the at least one miR gene product in the sample to a control, wherein an increase in the level of the at least one miR gene product in the sample from the subject, relative to that of the control, is diagnostic or prognostic of cancer and/or a myeloproliferative disorder, and wherein the at least one miR gene product is selected from the group consisting of miR- 101, miR-126, miR-99a, miR-99-prec, miR-106, miR-339, miR-99b, miR-149, miR-33, miR- 135 and miR-20.

2. The method of Claim 1, wherein the at least one miR gene product is selected from the group consisting of miR-101, miR-126, miR-106, miR-20 and miR-135.

3. The method of Claim 1, wherein the at least one miR gene product is selected from the group consisting of miR-106, miR-20 and miR-135.

4. The method of Claim 1, wherein the cancer and/or a myeloproliferative disorder is a cancer.

5. The method of Claim 4, wherein the cancer is a leukemia.

6. The method of Claim 5, wherein the leukemia is acute myeloid leukemia.

7. The method of Claim 6, wherein the acute myeloid leukemia is acute megakaryoblastic leukemia.

8. The method of Claim 4, wherein the cancer is multiple myeloma.

9. The method of Claim 1, wherein the cancer and/or a myeloproliferative disorder is a myeloproliferative disorder.

10. The method of Claim 9, wherein the myeloproliferative disorder is selected from the group consisting of essential thrombocytemia (ET), polycythemia vera (PV), myelodisplasia, myelofibrosis and chronic myelogenous leukemia (CML).

11. The method of Claim 1, wherein the control is selected from the group consisting of: i) a reference standard; ii) the level of the at least one miR gene product from a subject that does not have cancer and/or a myeloproliferative disorder; and iii) the level of the at least one miR gene product from a sample of the subject that is non-cancerous and/or does not exhibit a myeloproliferative disorder.

12. The method of Claim 1, wherein the subject is a human.

13. A method of treating a cancer and/or a myeloproliferative disorder in a subject, comprising administering to the subject an effective amount of a compound for inhibiting expression of at least one miR gene product, wherein the at least one miR gene product is selected from the group consisting of miR-101, miR-126, miR-99a, miR-99-prec, miR-106, miR-339, miR-99b, miR-149, miR-33, miR-135 and miR-20.

14. The method of Claim 13, wherein the at least one miR gene product is selected from the group consisting of miR-101, miR-126, miR-106, miR-20 and miR-135.

15. The method of Claim 13, wherein the at least one miR gene product is selected from the group consisting of miR-106, miR-20 and miR-135.

16. The method of Claim 13, wherein the cancer and/or a myeloproliferative disorder is a cancer.

17. The method of Claim 16, wherein the cancer is a leukemia.

18. The method of Claim 17, wherein the leukemia is acute myeloid leukemia.

19. The method of Claim 18, wherein the acute myeloid leukemia is acute megakaryoblastic leukemia.

20. The method of Claim 16, wherein the cancer is multiple myeloma.

21. The method of Claim 13, wherein the cancer and/or a myeloproliferative disorder is a myeloproliferative disorder.

22. The method of Claim 21, wherein the myeloproliferative disorder is selected from the group consisting of essential thrombocytemia (ET), polycythemia vera (PV), myelodisplasia, myelofibrosis and chronic myelogenous leukemia (CML).

23. The method of Claim 13, wherein the subject is a human.

24. A method of treating a cancer and/or a myeloproliferative disorder in a subject comprising administering an effective amount of at least one miR gene product or an isolated variant or biologically-active fragment thereof to the subject, wherein: the cancer and/or myeloproliferative disorder is associated with overexpression of a MAFB gene product; and the at least one miR gene product binds to, and decreases expression of, the MAFB gene product.

25. The method of Claim 24, wherein the at least one miR gene product or isolated variant or biologically-active fragment thereof comprises a nucleotide

sequence that is complementary to a nucleotide sequence in the MAFB gene product.

26. The method of Claim 25, wherein the at least one miR gene product is miR- 130a or an isolated variant or biologically-active fragment thereof.

27. The method of Claim 24, wherein the cancer and/or a myeloproliferative disorder is a cancer.

28. The method of Claim 27, wherein the cancer is a leukemia.

29. The method of Claim 28 wherein the leukemia is acute myeloid leukemia.

30. The method of Claim 29, wherein the acute myeloid leukemia is acute megakaryoblastic leukemia.

31. The method of Claim 27, wherein the cancer is multiple myeloma.

32. The method of Claim 24, wherein the cancer and/or a myeloproliferative disorder is a myeloproliferative disorder.

33. The method of Claim 32, wherein the myeloproliferative disorder is selected from the group consisting of essential thrombocytemia (ET), polycythemia vera (PV), myelodisplasia, myelofibrosis and chronic myelogenous leukemia (CML).

34. The method of Claim 24, wherein the subject is a human.

35. A method of treating a cancer and/or a myeloproliferative disorder in a subject comprising administering an effective amount of at least one miR gene product or an isolated variant or biologically-active fragment thereof to the

subject, wherein: the cancer and/or myeloproliferative disorder is associated with overexpression of a HOXA1 gene product; and the at least one miR gene product binds to, and decreases expression of, the HOXA1 gene product.

36. The method of Claim 35, wherein the at least one miR gene product or isolated variant or biologically-active fragment thereof comprises a nucleotide sequence that is complementary to a nucleotide sequence in the HOXA1 gene product.

37. The method of Claim 36, wherein the at least one miR gene product is miR-1 Oa or an isolated variant or biologically-active fragment thereof.

38. The method of Claim 35, wherein the cancer and/or a myeloproliferative disorder is a cancer.

39. The method of Claim 38, wherein the cancer is a leukemia.

40. The method of Claim 39, wherein the leukemia is acute myeloid leukemia.

41. The method of Claim 40, wherein the acute myeloid leukemia is acute megakaryoblastic leukemia.

42. The method of Claim 38, wherein the cancer is multiple myeloma.

43. The method of Claim 35, wherein the cancer and/or a myeloproliferative disorder is a myeloproliferative disorder. .

44. The method of Claim 43, wherein the myeloproliferative disorder is selected from the group consisting of essential thrombocytemia (ET)3 polycythemia vera (PV), myelodisplasia, myelofibrosis and chronic myelogenous leukemia (CML).

45. The method of Claim 35, wherein the subject is a human.

46. A method of determining and/or predicting megakaryocytic differentiation comprising: i) determining the level of at least one miR gene product in a sample comprising megakaryocyte progeny and/or megakaryocytes; and ii) comparing the level of the at least one miR gene product in the sample to a control, wherein an alteration in the level of the at least one miR gene product in the sample, relative to that of the control, is indicative of megakaryocytic differentiation.

47. The method of Claim 46 wherein the alteration is a decrease in the level of the at least one miR gene product in the sample.

48. The method of Claim 46, wherein the at least one miR gene product is selected from the group consisting of miR-10a, miR-126, miR-106, miR-010b, miR-130a, miR-130a- prec, miR-124a, miR-032-prec, miR-101, miR-30c, miR-213, miR-132-prec, miR-150, miR- 020, miR-339, let-7a, let-7d, miR-181c, miR-181b and miR-017.

49. The method of Claim 46, wherein the at least one miR gene product is selected from the group consisting of miR-lOa, miR-lOb, miR-30c, miR-106, miR-126, miR-130a, miR-132, and miR-143.

50. The method of Claim 46, wherein said sample is from a subject.

51. The method of Claim 50, wherein the subject is a human.

52. The method of Claim 1 , wherein the control is selected from the group consisting of: i) a reference standard; and ii) the level of the at least one miR gene product from a reference sample comprising non-differentiating megakaryocyte progeny and/or megakaryocytes.

53. A pharmaceutical composition for treating a cancer and/or a myeloproliferative disorder comprising an effective amount of a compound for inhibiting expression of at least one miR gene product and a pharmaceutically-acceptable carrier, wherein the at least one miR gene product is selected from the group consisting of miR-101, miR-126, miR-99a, miR-99- prec, miR-106, miR-339, miR-99b, miR-149, miR-33, miR-135 and miR-20.

54. The pharmaceutical composition of Claim 53, wherein the at least one miR gene product is selected from the group consisting of miR-101, miR-126, miR-106, miR-20, and miR-135.

55. The pharmaceutical composition of Claim 53, wherein the at least one miR gene product is selected from the group consisting of miR-106, miR-20 and miR-135.

56. The pharmaceutical composition of Claim 53, wherein the pharmaceutical composition further comprises at least one anti-cancer agent.

57. A pharmaceutical composition for treating a cancer associated with overexpression of a MAFB gene product and/or a myeloproliferative disorder associated with overexpression of a MAFB gene product comprising an effective amount of at least one miR gene product and a pharmaceutically-acceptable carrier, wherein the at least one miR gene product binds to, and decreases expression of, the MAFB gene product.

58. The pharmaceutical composition of Claim 57, wherein the at least one miR gene product comprises a nucleotide sequence that is complementary to a nucleotide sequence in the MAFB gene product.

59. The pharmaceutical composition of Claim 58, wherein the at least one miR gene product is miR- 130a or an isolated variant or biologically-active fragment thereof.

60. The pharmaceutical composition of Claim 57, wherein the pharmaceutical composition further comprises at least one anti-cancer agent.

61. A pharmaceutical composition for treating a cancer associated with overexpression of a HOXA1 gene product and/or a myeloproliferative disorder associated with overexpression of a HOXA1 gene product comprising an effective amount of at least one miR gene product and a pharmaceutically-acceptable carrier, wherein the at least one miR gene product binds to, and decreases expression of, the HOXA1 gene product.

62. The pharmaceutical composition of Claim 61, wherein the at least one miR gene product comprises a nucleotide sequence that is complementary to a nucleotide sequence in the HOXA1 gene product.

63. The pharmaceutical composition of Claim 62, wherein the at least one miR gene product is miR-10a or an isolated variant or biologically-active fragment thereof.

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ucgacaacaa aucacagucu gccauauggc acaggccaug ccucuaca 108

<210> 22
<211> 110
<212> RNA
<213> Homo sapiens

<400> 22
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aucgacaaca aaucacaguc ugccauaugg cacaggccau gccucuacag 110

<210> 23
<211> 110
<212> RNA
<213> Homo sapiens

<400> 23
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acugcgcuca acaacaaauc ccagucuacc uaauggugcc agccaucgca 110

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<211> 110
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uacuacgaca acaagucaca gccggccuca uagcgcagac ucccuucgac 110

<210> 25
<211> 89
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<400> 25
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cuagauaacc gaaaguaaaa auaacccca 89

<210> 26
<211> 87
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<400> 26
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agauaaccga aaguaaaaac uccuuca 87

<210> 27
<211> 90
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<400> 27
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cuagauaacc gaaaguagaa augauucuca 90

<210> 28
<211> 110
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<400> 28
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cacaaauucg uaucuagggg aauauguagu ugacauaaac acuccgcucu 110

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<211> 110
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<400> 29
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uagucacaga uucgauucua ggggaauaua uggucgaugc aaaaacuuca 110

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<211> 108
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<213> Homo sapiens

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uguggauuuu gaaaaggugc aggccauauu gugcugccuc aaaaauac 108

<210> 31
<211> 83
<212> RNA
<213> Homo sapiens

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ugugcugccu caaaaauaca agg 83

<210> 32
<211> 64
<212> RNA
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<400> 32
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cuag 64

<210> 33
<211> 98
<212> RNA
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<400> 33
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aucauuauuu gcugcucuag aaauuuaagg aaauucau 98

<210> 34
<211> 89
<212> RNA
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<400> 34
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auuaacugug cugcugaagu aagguugac 89

<210> 35
<211> 81
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<400> 35
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acugugcugc uuuaguguga c 81

<210> 36
<211> 81
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acugugcugc ugaaguaagg u 81

<210> 37
<211> 84
<212> RNA
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<400> 37
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aggcacuugu agcauuaugg ugac 84

<210> 38
<211> 71
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<400> 38
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uccuucuggc a 71

<210> 39
<211> 81
<212> RNA
<213> Homo sapiens

<400> 39
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gugcuccuuc uggcauaaga a 81

<210> 40
<211> 82
<212> RNA
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<400> 40
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ugcaaaacug augguggccu gc 82

<210> 41
<211> 80
<212> RNA
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<400> 41
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gcaaaacuga ugguggccug 80

<210> 42
<211> 87
<212> RNA
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<400> 42
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auccaugcaa aacugacugu gguagug 87

<210> 43
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cugugcaaau ccaugcaaaa cugauuguga uaaugu 96

<210> 44
<211> 80
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<400> 44
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ugcaaaacug acugugguag 80

<210> 45
<211> 81
<212> RNA
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<400> 45
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ccaugcaaaa cugauuguga u 81

<210> 46
<211> 71
<212> RNA
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<400> 46
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uaaaguacug c 71

<210> 47
<211> 72
<212> RNA
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<400> 47
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ggcugucuga ca 72

<210> 48
<211> 81
<212> RNA
<213> Homo sapiens

<400> 48
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gaugggcugu cugacauuuu g 81

<210> 49
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aguugaagaa cuguugcccu cugcc 85

<210> 50
<211> 73
<212> RNA
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<400> 50
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uuuccaaccg acc 73

<210> 51
<211> 97
<212> RNA
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<400> 51
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acauugccag ggauuaccac gcaaccacga ccuuggc 97

<210> 52
<211> 81
<212> RNA
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<400> 52
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gggauuucca accgacccug a 81

<210> 53
<211> 68
<212> RNA
<213> Homo sapiens

<400> 53
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aacaggag 68

<210> 54
<211> 73
<212> RNA
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<400> 54
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agcaggaaca ggg 73

<210> 55
<211> 81
<212> RNA
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<400> 55
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ucaguucagc aggaacaggg g 81

<210> 56
<211> 71
<212> RNA
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<400> 56
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ggaacagcau c 71

<210> 57
<211> 84
<212> RNA
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<400> 57
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ugucucgguc ugacagugcc ggcc 84

<210> 58
<211> 86
<212> RNA
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<400> 58
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gguuacuugc acggggacgc gggccu 86

<210> 59
<211> 77
<212> RNA
<213> Homo sapiens

<400> 59
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uacuugcacg gggacgc 77

<210> 60
<211> 84
<212> RNA
<213> Homo sapiens

<400> 60
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gauuacuugu uucuggaggc agcu 84

<210> 61
<211> 77

<212> RNA
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cuuggcucgg ggaccgg 77

<210> 62
<211> 78
<212> RNA
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<400> 62
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cuaaguuccg ccccccag 78

<210> 63
<211> 73
<212> RNA
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<400> 63
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aaguucugca ccu 73

<210> 64
<211> 97
<212> RNA
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uucacagugg cuaaguucug caccugaaga gaaggug 97

<210> 65
<211> 80
<212> RNA
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<400> 65
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gcuaaguucc gccccccagg 80

<210> 66
<211> 86
<212> RNA
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<400> 66
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uugugagcuc cuggagggca ggcacu 86

<210> 67
<211> 108
<212> RNA
<213> Homo sapiens

<400> 67
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ucuagcacca ucugaaaucg guuauaauga uuggggaaga gcaccaug 108

<210> 68
<211> 64
<212> RNA
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<400> 68
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uuau 64

<210> 69
<211> 81
<212> RNA
<213> Homo sapiens

<400> 69
cuucaggaag cuggguuucau auggugguuu agauuuaaau agugauuguc uagcaccauu 60

ugaaaucagu guucuugggg g 81

<210> 70
<211> 81
<212> RNA
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<400> 70
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uugaaaucag uguuuuagga g 81

<210> 71
<211> 110
<212> RNA
<213> Homo sapiens

<400> 71
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ugucuagcac cauuugaaau cgguuaugau guagggggaa aagcagcagc 110

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<211> 71
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uuugcagcug c 71

<210> 73
<211> 60
<212> RNA
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<400> 73

auguaaacau ccuacacuca gcuguaauac auggauuggc ugggaggugg auguuuacgu 60

<210> 74
<211> 88
<212> RNA
<213> Homo sapiens

<400> 74
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gguggauguu uacuucagcu gacuugga 88

<210> 75
<211> 72
<212> RNA
<213> Homo sapiens

<400> 75
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uuuacucuuu cu 72

<210> 76
<211> 70
<212> RNA
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<400> 76
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uugcugcuac 70

<210> 77
<211> 64
<212> RNA
<213> Homo sapiens

<400> 77
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acag 64

<210> 78
<211> 71
<212> RNA
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<400> 78
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gccaucuuuc c 71

<210> 79
<211> 70
<212> RNA
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<400> 79
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ugauauuuuc 70

<210> 80
<211> 110
<212> RNA
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<400> 80
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gcgggugcag ugccucggca gugcagcccg gagccggccc cuggcaccac 110

<210> 81
<211> 88
<212> RNA
<213> Homo sapiens

<400> 81
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gguggauguu uacuucagcu gacuugga 88

<210> 82
<211> 69
<212> RNA
<213> Homo sapiens

<400> 82
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gcaucacag 69

<210> 83
<211> 110
<212> RNA
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<400> 83
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aagcaaucag caaguauacu gcccuagaag ugcugcacgu ugugggggccc 110

<210> 84
<211> 84
<212> RNA
<213> Homo sapiens

<400> 84
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uccacugcca ucaaaacaag gcac 84

<210> 85
<211> 77
<212> RNA
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<400> 85
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ggccagguaa aaagauu 77

<210> 86

<211> 82
<212> RNA
<213> Homo sapiens

<400> 86
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ggcacuugua gcauuauggu ga 82

<210> 87
<211> 78
<212> RNA
<213> Homo sapiens

<400> 87
cuuucuacac agguuggggau cgguugcaau gcuguguuuc uguaugguau ugcacuuguc 60

ccggccuguu gaguuugg 78

<210> 88
<211> 75
<212> RNA
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<400> 88
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ccggccugug gaaga 75

<210> 89
<211> 80
<212> RNA
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<400> 89
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agcacuuccc gagccccccgg 80

<210> 90
<211> 81
<212> RNA
<213> Homo sapiens

<400> 90
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uuauugagca cccacucugu g 81

<210> 91
<211> 78
<212> RNA
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cagugccaau augggaaa 78

<210> 92
<211> 80
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<213> Homo sapiens

<400> 92
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gauguuugca gcugccuacu 80

<210> 93
<211> 80
<212> RNA
<213> Homo sapiens

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uauacaacuu acuacuuucc 80

<210> 94
<211> 70
<212> RNA
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<400> 94
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gguccguguc 70

<210> 95
<211> 81
<212> RNA
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<400> 95
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cuaugggucu gugucagugu g 81

<210> 96
<211> 108
<212> RNA
<213> Homo sapiens

<400> 96
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uccgcacaag cuuguaucua uagguaugug ucuguuaggc aaucucac 108

<210> 97
<211> 80
<212> RNA
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<400> 97
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auagguaugu gucuguuagg 80

<210> 98
<211> 110
<212> RNA
<213> Homo sapiens

<400> 98
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ugauaacuga aggauggcag ccaucuuacc uuccaucaga ggagccucac 110

<210> 99
<211> 57
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<210> 100
<211> 75
<212> RNA
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<400> 100
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aacugaagga uggca 75

<210> 101
<211> 79
<212> RNA
<213> Homo sapiens

<400> 101
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auaacugaag aaugguggu 79

<210> 102
<211> 75
<212> RNA
<213> Homo sapiens

<400> 102
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aacugaagaa uggug 75

<210> 103
<211> 81
<212> RNA
<213> Homo sapiens

<400> 103
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uugaaaucag uguuuuagga g 81

<210> 104
<211> 81
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<400> 104
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ugaaaucagu guucuuggggg g 81

<210> 105
<211> 78
<212> RNA
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<400> 105
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agggcuauga aagaacca 78

<210> 106
<211> 78
<212> RNA
<213> Homo sapiens

<400> 106
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agggcuauga aggcauug 78

<210> 107
<211> 78
<212> RNA
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<400> 107
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auaagcuacc cgacaagg 78

<210> 108
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<400> 108
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gagcaugugc uacggugucu a 81

<210> 109
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<400> 109
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gagcaugugc uauggugucu a 81

<210> 110
<211> 81
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gcacuucuua cauuaccaug g 81

<210> 111
<211> 82
<212> RNA
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<400> 111
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ggguacuugc ugcuccagca gg 82

<210> 112
<211> 81
<212> RNA
<213> Homo sapiens

<400> 112
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acagggcuau caaagcacag a 81

<210> 113
<211> 90
<212> RNA
<213> Homo sapiens

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ccccugaaag ucccucauuu uucuugcugu 90

<210> 114
<211> 80
<212> RNA
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<400> 114
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ccccaaaagu cccucauuuu 80

<210> 115
<211> 85
<212> RNA
<213> Homo sapiens

<400> 115
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ucacacuaaa uagcuacugc uaggc 85

<210> 116
<211> 66
<212> RNA
<213> Homo sapiens

<400> 116
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auagcu 66

<210> 117
<211> 61

<212> RNA
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<400> 117
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<210> 118
<211> 85
<212> RNA
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<400> 118
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gcggugaaug ccaagaaugg ggcug 85

<210> 119
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uuaaggcacg cggugaaugc caagagcgga gccuacggcu gcacuugaag 110

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<211> 87
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<400> 120
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gcggugaaug ccaagagagg cgccucc 87

<210> 121
<211> 68
<212> RNA
<213> Homo sapiens

<400> 121
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gccaagag 68

<210> 122
<211> 67
<212> RNA
<213> Homo sapiens

<400> 122
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ccaagag 67

<210> 123
<211> 86
<212> RNA
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<400> 123
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gguucuuggg agccuggcgu cuggcc 86

<210> 124
<211> 65
<212> RNA
<213> Homo sapiens

<400> 124
ggucccugag acccuuuaac cugugaggac auccaggguc acaggugagg uucuugggag 60

ccugg 65

<210> 125
<211> 88
<212> RNA
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<400> 125
ugcgcuccuc ucagucccug agacccuaac uugugauguu uaccguuuaa auccacgggu 60

uaggcucuug ggagcugcga gucgugcu 88

<210> 126
<211> 89
<212> RNA
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<400> 126
accagacuuu uccuaguccc ugagacccua acuugugagg uauuuuagua acaucacaag 60

ucaggcucuu gggaccuagg cggagggga 89

<210> 127
<211> 85
<212> RNA
<213> Homo sapiens

<400> 127
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gaguaauaau gcgccgucca cggca 85

<210> 128
<211> 61
<212> RNA
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<400> 128
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<210> 129
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<212> RNA
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<400> 129

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auccgucuga gcuuggcugg ucggaagucu caucauc 97

<210> 130
<211> 70
<212> RNA
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<400> 130
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ggcuggucgg 70

<210> 131
<211> 82
<212> RNA
<213> Homo sapiens

<400> 131
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cggucucuuu uucagcugcu uc 82

<210> 132
<211> 110
<212> RNA
<213> Homo sapiens

<400> 132
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ggucucacag ugaaccgguc ucuuucccua cugugucaca cuccuaaugg 110

<210> 133
<211> 70
<212> RNA
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cuuuuucagc 70

<210> 134
<211> 74
<212> RNA
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ccaaaaagua ucua 74

<210> 135
<211> 90
<212> RNA
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<400> 135
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ccuuacccca aaaagcauuu gcggagggcg 90

<210> 136
<211> 89
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<400> 136
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aauguuaaaa gggcauuggc cguguagug 89

<210> 137
<211> 110
<212> RNA
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<400> 137
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uucauaaagc uagauaaccg aaaguaaaaa uaaccccaua cacugcgcag 110

<210> 138
<211> 110
<212> RNA
<213> Homo sapiens

<400> 138
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uaugagugcc acagagccgu cauaaagcua gauaaccgaa aguagaaaug 110

<210> 139
<211> 72
<212> RNA
<213> Homo sapiens

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gaaaguaaaa ac 72

<210> 140
<211> 101
<212> RNA
<213> Homo sapiens

<400> 140
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acagucuaca gccauggucg ccccgcagca cgcccacgcg c 101

<210> 141
<211> 66
<212> RNA
<213> Homo sapiens

<400> 141
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ucgccc 66

<210> 142
<211> 88
<212> RNA
<213> Homo sapiens

<400> 142
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ccuucaacca gcuguagcua ugcauuga 88

<210> 143
<211> 102
<212> RNA
<213> Homo sapiens

<400> 143
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uggucccuu caaccagcug uagcugugca uugauggcgc cg 102

<210> 144
<211> 68
<212> RNA
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<400> 144
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gcuguagc 68

<210> 145
<211> 119
<212> RNA
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<400> 145
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agagguuugg uccccuucaa ccagcuacag cagggcuggc aaugcccagu ccuuggaga 119

<210> 146
<211> 80
<212> RNA
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<400> 146
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uucaaccagc uacagcaggg 80

<210> 147
<211> 73
<212> RNA
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<400> 147
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gucaccaacc cuc 73

<210> 148

<211> 71
<212> RNA
<213> Homo sapiens

<400> 148
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ucaccaaccc u 71

<210> 149
<211> 90
<212> RNA
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<400> 149
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ggauuggagc cguggcgcac ggcggggaca 90

<210> 150
<211> 100
<212> RNA
<213> Homo sapiens

<400> 150
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auguagggau ggaagccaug aaauacauug ugaaaaauca 100

<210> 151
<211> 60
<212> RNA
<213> Homo sapiens

<400> 151
cuauggcuuu uuauuccuau gugauucuac ugcucacuca uauagggauu ggagccgugg 60

<210> 152
<211> 97
<212> RNA
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<400> 152
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ggcuaaaagc caugggcuac agugaggggc gagcucc 97

<210> 153
<211> 82
<212> RNA
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<400> 153
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aaaugagucu ucagaggguu cu 82

<210> 154
<211> 62
<212> RNA
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<400> 154
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<210> 155
<211> 73
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cgcguagucg agg 73

<210> 156
<211> 99
<212> RNA
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<400> 156
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cggcuacuuc acaacaccag ggccacacca cacuacagg 99

<210> 157
<211> 84
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<400> 157
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uuucacgaca ccaggguugc auca 84

<210> 158
<211> 71
<212> RNA
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<400> 158
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caccaggguu g 71

<210> 159
<211> 68
<212> RNA
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ggaguaac 68

<210> 160
<211> 100
<212> RNA
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<400> 160
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cuaccacagg guagaaccac ggacaggaua ccggggcacc 100

<210> 161
<211> 72
<212> RNA
<213> Homo sapiens

<400> 161
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ccacggacag ga 72

<210> 162
<211> 70
<212> RNA
<213> Homo sapiens

<400> 162
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cacggacagg 70

<210> 163
<211> 95
<212> RNA
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<400> 163
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acacugucug guaaagaugg cucccgggug gguuc 95

<210> 164
<211> 72
<212> RNA
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<400> 164
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uaaagauggc cc 72

<210> 165
<211> 64
<212> RNA
<213> Homo sapiens

<400> 165
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gaug 64

<210> 166
<211> 106
<212> RNA
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<400> 166
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ugagaugaag cacuguagcu caggaagaga gaaguuguuc ugcagc 106

<210> 167
<211> 63
<212> RNA
<213> Homo sapiens

<400> 167
ccugaggugc agugcugcau cucuggucag uugggagucu gagaugaagc acuguagcuc 60

agg 63

<210> 168
<211> 86
<212> RNA
<213> Homo sapiens

<400> 168
uggggcccug gcugggauau caucauauac uguaaguuug cgaugagaca cuacaguaua 60

gaugauguac uaguccgggc accccc 86

<210> 169
<211> 66
<212> RNA
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<400> 169
ggcugggaua ucaucauaua cuguaaguuu gcgaugagac acuacaguau agaugaugua 60

cuaguc 66

<210> 170
<211> 88
<212> RNA
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<400> 170
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uggaaauacu guucuugagg ucaugguu 88

<210> 171
<211> 70
<212> RNA
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<400> 171
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uguucuugag 70

<210> 172
<211> 99
<212> RNA
<213> Homo sapiens

<400> 172
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ugaaauucag uucuucagcu gggauaucuc ugucaucgu 99

<210> 173
<211> 65
<212> RNA
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<400> 173
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cagcu 65

<210> 174
<211> 72
<212> RNA
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<400> 174
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uucugcuaga uu 72

<210> 175
<211> 68
<212> RNA
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<400> 175
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uuugucuc 68

<210> 176
<211> 99
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<400> 176
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agucagugca ucacagaacu uugucucgaa agcuuucua 99

<210> 177
<211> 70
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<400> 177
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gucagugcau 70

<210> 178
<211> 89
<212> RNA
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<400> 178
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gggacggggg cugugcuggg gcagcugga 89

<210> 179
<211> 53

<212> RNA
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<400> 179
gcucuggcuc cgugucuuca cucccgugcu uguccgagga gggagggagg gac 53

<210> 180
<211> 84
<212> RNA
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<400> 180
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ccugggggac agggaccugg ggac 84

<210> 181
<211> 64
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<400> 181
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aggg 64

<210> 182
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<212> RNA
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cuugaggaca gg 72

<210> 183
<211> 69
<212> RNA
<213> Homo sapiens

<400> 183
ccuguccuca aggagcuuca gucuaguagg ggaugagaca uacuagacug ugagcuccuc 60

gagggcagg 69

<210> 184
<211> 87
<212> RNA
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<400> 184
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augacagaac uugggcccgg aaggacc 87

<210> 185
<211> 71
<212> RNA
<213> Homo sapiens

<400> 185

ggcccagguu cugugauaca cuccgacucg ggcucuggag cagucagugc augacagaac 60

uugggccccg g 71

<210> 186
<211> 90
<212> RNA
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<400> 186
cucacagcug ccagugucau uuuugugauc ugcagcuagu auucucacuc caguugcaua 60

gucacaaaag ugaucauugg caggugguggc 90

<210> 187
<211> 71
<212> RNA
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<400> 187
ucucucucuc ccucacagcu gccaguguca uugucacaaa agugaucauu ggcaggugug 60

gcugcugcau g 71

<210> 188
<211> 87
<212> RNA
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ucacaaaagu gaucauugga aacugug 87

<210> 189
<211> 69
<212> RNA
<213> Homo sapiens

<400> 189
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ugaucauug 69

<210> 190
<211> 84
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<400> 190
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gguugaccua uuuuucagua ccaa 84

<210> 191
<211> 66
<212> RNA
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<400> 191
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auuuuu 66

<210> 192
<211> 65
<212> RNA
<213> Homo sapiens

<400> 192
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aacag 65

<210> 193
<211> 82
<212> RNA
<213> Homo sapiens

<400> 193
ccuaacacug ucugguaaag auggcucccg gguggguucu cucggcagua accuucaggg 60

agcccugaag accauggagg ac 82

<210> 194
<211> 110
<212> RNA
<213> Homo sapiens

<400> 194
gccgagaccg agugcacagg gcucugaccu augaauugac agccagugcu cucgucuccc 60

cucuggcugc caauuccaua ggucacaggu auguucgccu caaugccagc 110

<210> 195
<211> 80
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guuaucuggg gcgagggcca 80

<210> 196
<211> 70
<212> RNA
<213> Homo sapiens

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ggcgcucggg 70

<210> 197
<211> 64
<212> RNA
<213> Homo sapiens

<400> 197
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aauu 64

<210> 198
<211> 70
<212> RNA
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<400> 198
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ggaauuuuuu 70

<210> 199
<211> 108
<212> RNA
<213> Homo sapiens

<400> 199
caaugucagc agugccuuag cagcacguaa auauuggcgu uaagauucua aaauuaucuc 60

caguauuaac ugugcugcug aaguaagguu gaccauacuc uacaguug 108

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<211> 81
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gcccuaguga cuacaaagcc c 81

<210> 201
<211> 70
<212> RNA
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<400> 201
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aaagcucauu 70

<210> 202
<211> 70
<212> RNA
<213> Homo sapiens

<400> 202
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cuuccacaac 70

<210> 203
<211> 110
<212> RNA
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<400> 203
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uuugggauuu gaaaaaacca cugaccguug acuguaccuu gggguccuua 110

<210> 204

<211> 110
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<400> 204
ccugugcaga gauuauuuuu uaaaagguca caaucaacau ucauugcugu cgguggguug 60

aacugugugg acaagcucac ugaacaauga augcaacugu ggccccgcuu 110

<210> 205
<211> 89
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<400> 205
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aucaaugaau gcaaacugcg gaccaaaca 89

<210> 206
<211> 110
<212> RNA
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<400> 206
cggaaaauuu gccaaggguu ugggggaaca uucaaccugu cggugaguuu gggcagcuca 60

ggcaaaccau cgaccguuga guggacccug aggccuggaa uugccauccu 110

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<211> 110
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<400> 207
gagcugcuug ccucccccccg uuuuuggcaa ugguagaacu cacacuggug agguaacagg 60

auccgguggu ucuagacuug ccaacuaugg ggcgaggacu cagccggcac 110

<210> 208
<211> 70
<212> RNA
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<400> 208
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ccaacuaugg 70

<210> 209
<211> 110
<212> RNA
<213> Homo sapiens

<400> 209
ccgcagagug ugacuccugu ucuguguaug gcacugguag aauucacugu gaacagucuc 60

agucagugaa uuaccgaagg gccauaaaca gagcagagac agauccacga 110

<210> 210
<211> 84
<212> RNA

<213> Homo sapiens

<400> 210
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gaacugauaa ggguagguga uuga 84

<210> 211
<211> 65
<212> RNA
<213> Homo sapiens

<400> 211
ccuuaucacu uuuccagccc agcuuuguga cuguaagugu uggacggaga acugauaagg 60

guagg 65

<210> 212
<211> 82
<212> RNA
<213> Homo sapiens

<400> 212
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uuccucuggu ccuucccucc ca 82

<210> 213
<211> 66
<212> RNA
<213> Homo sapiens

<400> 213
agggauugga gagaaaggca guuccugaug gucccccuccc caggggcugg cuuuccucug 60

guccuu 66

<210> 214
<211> 86
<212> RNA
<213> Homo sapiens

<400> 214
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ggugaauuuu uugggaaguu ugagcu 86

<210> 215
<211> 71
<212> RNA
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<400> 215
acuuuccaaa gaauucuccu uuugggcuuu cuggguuuau uuuaagccca aaggugaauu 60

uuuugggaag u 71

<210> 216
<211> 109
<212> RNA
<213> Homo sapiens

<400> 216
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cucugacccc ucgugucuug uguugcagcc ggagggacgc agguccgca 109

<210> 217
<211> 86
<212> RNA
<213> Homo sapiens

<400> 217
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augcaggguu ugcaggaugg cgagcc 86

<210> 218
<211> 68
<212> RNA
<213> Homo sapiens

<400> 218
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uugcagga 68

<210> 219
<211> 102
<212> RNA
<213> Homo sapiens

<400> 219
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cuggcucagu ucagcaggaa caggagucga gcccuugagc aa 102

<210> 220
<211> 68
<212> RNA
<213> Homo sapiens

<400> 220
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aacaggag 68

<210> 221
<211> 85
<212> RNA
<213> Homo sapiens

<400> 221
ugcaggccuc ugugugauau guuugauaua uuagguuguu auuuaaucca acuauauauc 60

aaacauauuc cuacaguguc uugcc 85

<210> 222
<211> 67
<212> RNA
<213> Homo sapiens

<400> 222
cugugugaua uguuugauau auuagguugu uauuuaaucc aacuauauau caaacauauu 60

ccuacag 67

<210> 223
<211> 92
<212> RNA
<213> Homo sapiens

<400> 223
cggcuggaca gcgggcaacg gaaucccaaa agcagcuguu gucuccagag cauuccagcu 60

gcgcuuggau uucgucccu gcucuccugc cu 92

<210> 224
<211> 74
<212> RNA
<213> Homo sapiens

<400> 224
agcgggcaac ggaaucccaa aagcagcugu ugucuccaga gcauuccagc ugcgcuugga 60

uuucgucccc ugcu 74

<210> 225
<211> 108
<212> RNA
<213> Homo sapiens

<400> 225
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ucuggcugcc aauuccauag gucacaggua uguucgccuc aaugccag 108

<210> 226
<211> 110
<212> RNA
<213> Homo sapiens

<400> 226
gccgagaccg agugcacagg gcucugaccu augaauugac agccagugcu cucgucuccc 60

cucuggcugc caauuccaua ggucacaggu auguucgccu caaugccagc 110

<210> 227
<211> 88
<212> RNA
<213> Homo sapiens

<400> 227
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ccuacaaagu cccaguucuc ggcccccg 88

<210> 228
<211> 58
<212> RNA
<213> Homo sapiens

<400> 228
gcugggucuu ugcgggcgag augagggugu cggaucaacu ggccuacaaa gucccagu 58

<210> 229
<211> 85
<212> RNA
<213> Homo sapiens

<400> 229
augguguuau caaguguaac agcaacucca uguggacugu guaccaauuu ccaguggaga 60

ugcuguuacu uuugaugguu accaa 85

<210> 230
<211> 63
<212> RNA
<213> Homo sapiens

<400> 230
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gau 63

<210> 231
<211> 87
<212> RNA
<213> Homo sapiens

<400> 231
agcuucccug gcucuagcag cacagaaaua uuggcacagg gaagcgaguc ugccaauauu 60

ggcugugcug cuccaggcag gguggug 87

<210> 232
<211> 58
<212> RNA
<213> Homo sapiens

<400> 232
uagcagcaca gaaauauugg cacagggaag cgagucugcc aauauuggcu gugcugcu 58

<210> 233
<211> 110
<212> RNA
<213> Homo sapiens

<400> 233
cuagagcuug aauuggaacu gcugagugaa uuagguaguu ucauguuguu gggccugggu 60

uucugaacac aacaacauua aaccacccga uucacggcag uuacugcucc 110

<210> 234
<211> 70
<212> RNA
<213> Homo sapiens

<400> 234
gugaauuagg uaguuucaug uuguugggcc uggguuucug aacacaacaa cauuaaacca 60

cccgauucac 70

<210> 235
<211> 110
<212> RNA
<213> Homo sapiens

<400> 235
ugcucgcuca gcugaucugu ggcuuaggua guuucauguu guugggauug aguuuugaac 60

ucggcaacaa gaaacugccu gaguuacauc agucgguuuu cgucgagggc 110

<210> 236
<211> 70
<212> RNA
<213> Homo sapiens

<400> 236
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cccgauucac 70

<210> 237
<211> 84
<212> RNA
<213> Homo sapiens

<400> 237
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acacugccuu cauuacuuca guug 84

<210> 238
<211> 75
<212> RNA
<213> Homo sapiens

<400> 238
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ccacccagca uggcc 75

<210> 239
<211> 60
<212> RNA
<213> Homo sapiens

<400> 239
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<210> 240
<211> 62
<212> RNA
<213> Homo sapiens

<400> 240
ucauuggucc agaggggaga uagguuccug ugauuuuucc uucuucucua uagaauaaau 60

ga 62

<210> 241
<211> 71
<212> RNA
<213> Homo sapiens

<400> 241
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auugguuagg c 71

<210> 242
<211> 110
<212> RNA
<213> Homo sapiens

<400> 242
aggaagcuuc uggagauccu gcuccgucgc cccaguguuc agacuaccug uucaggacaa 60

ugccguugua caguagucug cacauugguu agacugggca agggagagca 110

<210> 243
<211> 110
<212> RNA
<213> Homo sapiens

<400> 243
ccagaggaca ccuccacucc gucuacccag uguuuagacu aucuguucag gacucccaaa 60

uuguacagua gucugcacau uggguaggcu gggcuggguu agacccucgg 110

<210> 244
<211> 71
<212> RNA
<213> Homo sapiens

<400> 244
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auugguuagg c 71

<210> 245
<211> 70
<212> RNA
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<400> 245
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ugaugacggc 70

<210> 246
<211> 95
<212> RNA
<213> Homo sapiens

<400> 246
ccagcucggg cagccguggc caucuuacug ggcagcauug gauggaguca ggucucuaau 60

acugccuggu aaugaugacg gcggagcccu gcacg 95

<210> 247
<211> 68
<212> RNA
<213> Homo sapiens

<400> 247
cccucgucuu acccagcagu guuuggguge gguuggguagu cucuaauacu gccgguaau 60

gauggagg 68

<210> 248
<211> 72
<212> RNA
<213> Homo sapiens

<400> 248
guuccuuuuu ccuaugcaua uacuucuuug aggaucuggc cuaaagaggu auagggcaug 60

ggaagaugga gc 72

<210> 249
<211> 110
<212> RNA
<213> Homo sapiens

<400> 249
guguugggga cucgcgcgcu ggguccagug guucuuaaca guucaacagu ucuguagcgc 60

aauugugaaa uguuuaggac cacuagaccc ggcgggcgcg gcgacagcga 110

<210> 250
<211> 110
<212> RNA
<213> Homo sapiens

<400> 250
ggcuacaguc uuucuucaug ugacucgugg acuucccuuu gucauccuau gccugagaau 60

auaugaagga ggcugggaag gcaaagggac guucaauugu caucacuggc 110

<210> 251
<211> 110
<212> RNA
<213> Homo sapiens

<400> 251
aaagauccuc agacaaucca ugugcuucuc uuguccuuca uuccaccgga gucugucuca 60

uacccaacca gauuucagug gagugaaguu caggaggcau ggagcugaca 110

<210> 252
<211> 86
<212> RNA
<213> Homo sapiens

<400> 252
ugcuucccga ggccacaugc uucuuuauau ccccauaugg auuacuuugc uauggaaugu 60

aaggaagugu gugguuucgg caagug 86

<210> 253
<211> 69
<212> RNA
<213> Homo sapiens

<400> 253
aggccacaug cuucuuuaua uccccauaug gauuacuuug cuauggaaug uaaggaagug 60

ugugguuuu 69

<210> 254

<211> 71
<212> RNA
<213> Homo sapiens

<400> 254
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cuuguugguc a 71

<210> 255
<211> 110
<212> RNA
<213> Homo sapiens

<400> 255
acccggcagu gccuccaggc gcagggcagc cccugcccac cgcacacugc gcugccccag 60

acccacugug cgugugacag cggcugaucu gugccugggc agcgcgaccc 110

<210> 256
<211> 110
<212> RNA
<213> Homo sapiens

<400> 256
ucaccuggcc augugacuug ugggcuuccc uuugucaucc uucgccuagg gcucugagca 60

gggcagggac agcaaagggg ugcucaguug ucacuuccca cagcacggag 110

<210> 257
<211> 110
<212> RNA
<213> Homo sapiens

<400> 257
cggggcaccc cgcccggaca gcgcgccggc accuuggcuc uagacugcuu acugcccggg 60

ccgcccucag uaacagucuc cagucacggc caccgacgcc uggccccgcc 110

<210> 258
<211> 110
<212> RNA
<213> Homo sapiens

<400> 258
ccugugcaga gauuauuuuu uaaaagguca caaucaacau ucauugcugu cgguggguug 60

aacugugugg acaagcucac ugaacaauga augcaacugu ggccccgcuu 110

<210> 259
<211> 108
<212> RNA
<213> Homo sapiens

<400> 259
gaguuuugag guugcuucag ugaacauuca acgcugucgg ugaguuugga auuaaaauca 60

aaaccaucga ccguugauug uacccuaugg cuaaccauca ucuacucc 108

<210> 260
<211> 110
<212> RNA

<213> Homo sapiens

<400> 260
ggccuggcug gacagaguug ucaugugucu gccugucuac acuugcugug cagaacaucc 60

gcucaccugu acagcaggca cagacaggca gucacaugac aacccagccu 110

<210> 261
<211> 110
<212> RNA
<213> Homo sapiens

<400> 261
aucauucaga aaugguauac aggaaaauga ccuaugaauu gacagacaau auagcugagu 60

uugucuguca uuucuuuagg ccaauauucu guaugacugu gcuacuucaa 110

<210> 262
<211> 110
<212> RNA
<213> Homo sapiens

<400> 262
gauggcugug aguuggcuua aucucagcug gcaacuguga gauguucaua caaucccuca 60

caguggucuc ugggauuaug cuaaacagag caauuuccua gcccucacga 110

<210> 263
<211> 110
<212> RNA
<213> Homo sapiens

<400> 263
aguauaauua uuacauaguu uuugaugucg cagauacugc aucaggaacu gauuggauaa 60

gaaucaguca ccaucaguuc cuaaugcauu gccuucagca ucuaaacaag 110

<210> 264
<211> 110
<212> RNA
<213> Homo sapiens

<400> 264
gugauaaugu agcgagauuu ucuguugugc uugaucuaac caugugguug cgagguauga 60

guaaaacaug guuccgucaa gcaccaugga acgucacgca gcuuucuaca 110

<210> 265
<211> 110
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<213> Homo sapiens

<400> 265
gaccagucgc ugcggggcuu uccuuugugc uugaucuaac caugguggug aacgauggaa 60

acggaacaug guucugucaa gcaccgcgga aagcaccgug cucuccugca 110

<210> 266
<211> 110
<212> RNA
<213> Homo sapiens

<400> 266
ccgccccggg ccgcggcucc ugauugucca aacgcaauuc ucgagucuau ggcuccggcc 60

gagaguugag ucuggacguc ccgagccgcc gcccccaaac cucgagcggg 110

<210> 267
<211> 110
<212> RNA
<213> Homo sapiens

<400> 267
ccgccccggg ccgcggcucc ugauugucca aacgcaauuc ucgagucuau ggcuccggcc 60

gagaguugag ucuggacguc ccgagccgcc gcccccaaac cucgagcggg 110

<210> 268
<211> 97
<212> RNA
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<400> 268
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gagaauugug gcuggacauc uguggcugag cuccggg 97

<210> 269
<211> 110
<212> RNA
<213> Homo sapiens

<400> 269
gacagugugg cauuguaggg cuccacaccg uaucugacac uuugggcgag ggcaccaugc 60

ugaagguguu caugaugcgg ucugggaacu ccucacggau cuuacugaug 110

<210> 270
<211> 110
<212> RNA
<213> Homo sapiens

<400> 270
ugaacaucca ggucuggggc augaaccugg cauacaaugu agauuucugu guucguuagg 60

caacagcuac auugucugcu ggguuucagg cuaccuggaa acauguucuc 110

<210> 271
<211> 110
<212> RNA
<213> Homo sapiens

<400> 271
gcugcuggaa gguguaggua cccucaaugg cucaguagcc aguguagauc cugucuuucg 60

uaaucagcag cuacaucugg cuacuggguc ucugauggca ucuucuagcu 110

<210> 272
<211> 110
<212> RNA
<213> Homo sapiens

<400> 272
ccuggccucc ugcagugcca cgcuccgugu auuugacaag cugaguugga cacuccaugu 60

gguagagugu caguuuguca aauaccccaa gugcggcaca ugcuuaccag 110

<210> 273
<211> 81
<212> RNA
<213> Homo sapiens

<400> 273
gggcuuucaa gucacuagug guuccguuua guagaugauu gugcauuguu ucaaaauggu 60

gcccuaguga cuacaaagcc c 81

<210> 274
<211> 60
<212> RNA
<213> Homo sapiens

<400> 274
caaucuuccu uuaucauggu auugauuuuu cagugcuucc cuuuugugug agagaagaua 60

<210> 275
<211> 80
<212> RNA
<213> Homo sapiens

<400> 275
aggacccuuc cagagggccc ccccucaauc cuguugugcc uaauucagag gguuugggugg 60

aggcucuccu gaagggcucu 80

<210> 276
<211> 63
<212> RNA
<213> Homo sapiens

<400> 276
aagaaauggu uuaccguccc acauacauuu ugaauaugua ugugggaugg uaaaccgcuu 60

cuu 63

<210> 277
<211> 86
<212> RNA
<213> Homo sapiens

<400> 277
acugcuaacg aaugcucuga cuuuauugca cuacuguacu uuacagcuag cagugcaaua 60

guauugucaa agcaucugaa agcagg 86

<210> 278
<211> 69
<212> RNA
<213> Homo sapiens

<400> 278
ccaccacuua aacguggaug uacuugcuuu gaaacuaaag aaguaagugc uuccauguuu 60

uggugaugg 69

<210> 279
<211> 73
<212> RNA
<213> Homo sapiens

<400> 279
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uuuuaguagg agu 73

<210> 280
<211> 68
<212> RNA
<213> Homo sapiens

<400> 280
ccuuugcuuu aacaugggggg uaccugcugu gugaaacaaa aguaagugcu uccauguuuc 60

aguggagg 68

<210> 281
<211> 68
<212> RNA
<213> Homo sapiens

<400> 281
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gagugugg 68

<210> 282
<211> 82
<212> RNA
<213> Homo sapiens

<400> 282
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agagggcgaa aaaggaugag gu 82

<210> 283
<211> 59
<212> RNA
<213> Homo sapiens

<400> 283
uuggccuccu aagccaggga uuguggguuc gagucccacc cgggguaaag aaaggccga 59

<210> 284
<211> 86
<212> RNA
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<400> 284
uugguacuug gagagaggug guccguggcg cguucgcuuu auuuauggcg cacauuacac 60

ggucgaccuc uuugcaguau cuaauc 86

<210> 285
<211> 83
<212> RNA
<213> Homo sapiens

<400> 285
cugacuaugc cucccccgcau ccccuagggc auugguguaa agcuggagac ccacugcccc 60

aggugcugcu ggggguugua guc 83

<210> 286
<211> 98
<212> RNA
<213> Homo sapiens

<400> 286
auacagugcu ugguuccuag uaggugucca guaaguguuu gugacauaau uuguuuauug 60

aggaccuccu aucaaucaag cacugugcua ggcucugg 98

<210> 287
<211> 95
<212> RNA
<213> Homo sapiens

<400> 287
cucaucuguc uguuugggcug gaggcagggc cuuugugaag gcgggguggug cucagaucgc 60

cucugggccc uuccuccagc cccgaggcgg auuca 95

<210> 288
<211> 75
<212> RNA
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<400> 288
uggaguggggg gggcaggagg ggcucaggga gaaagugcau acagccccug gcccucucug 60

cccuuccguc cccug 75

<210> 289
<211> 94
<212> RNA
<213> Homo sapiens

<400> 289
cuuuggcgau cacugccucu cugggccugu gucuuaggcu cugcaagauc aaccgagcaa 60

agcacacggc cugcagagag gcagcgcucu gccc 94

<210> 290
<211> 94
<212> RNA
<213> Homo sapiens

<400> 290
gaguuugguu uuguuugggu uuguucuagg uaugguccca gggaucccag aucaaaccag 60

gccccugggc cuauccuaga accaaccuaa gcuc 94

<210> 291
<211> 94
<212> RNA
<213> Homo sapiens

<400> 291

uguuuugagc gggggucaag agcaauaacg aaaaauguuu gucauaaacc guuuuucauu 60

auugcuccug accuccucuc auuugcuaua uuca 94

<210> 292
<211> 93
<212> RNA
<213> Homo sapiens

<400> 292
guagucagua guuggggggu gggaacggcu ucauacagga guugaugcac aguuauccag 60

cuccuauaug augccuuucu ucauccccuu caa 93

<210> 293
<211> 67
<212> RNA
<213> Homo sapiens

<400> 293
ucuccaacaa uauccuggug cugagugaug acucaggcga cuccagcauc agugauuuug 60

uugaaga 67

<210> 294
<211> 94
<212> RNA
<213> Homo sapiens

<400> 294
cggggcggcc gcucucccug uccuccagga gcucacgugu gccugccugu gagcgccucg 60

acgacagagc cggcgccugc cccagugucu gcgc 94

<210> 295
<211> 95
<212> RNA
<213> Homo sapiens

<400> 295
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gucucaguua cuuuauagcc auaccuggua ucuua 95

<210> 296
<211> 99
<212> RNA
<213> Homo sapiens

<400> 296
gaaacugggc ucaaggugag gggugcuauc ugugauugag ggacaugguu aauggaauug 60

ucucacacag aaaucgcacc cgucaccuug gccuacuua 99

<210> 297
<211> 98
<212> RNA
<213> Homo sapiens

<400> 297
acccaaaccc uaggucugcu gacuccuagu ccagggcucg ugauggcugg ugggcccuga 60

acgagggguc uggaggccug gguuugaaua ucgacagc 98

<210> 298
<211> 86
<212> RNA
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<400> 298
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agcugccugg gcagagcggc uccugc 86

<210> 299
<211> 68
<212> RNA
<213> Homo sapiens

<400> 299
ccauuacugu ugcuaauaug caacucuguu gaauauaaau uggaauugca cuuuagcaau 60
ggugaugg 68

<210> 300
<211> 66
<212> RNA
<213> Homo sapiens

<400> 300
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cguuuu 66

<210> 301
<211> 70
<212> RNA
<213> Homo sapiens

<400> 301
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cuuuucucag 70

<210> 302
<211> 75
<212> RNA
<213> Homo sapiens

<400> 302
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gaaccugguc ugucu 75

<210> 303
<211> 67
<212> RNA
<213> Homo sapiens

<400> 303
guggcacuca aacugugggg gcacuuucug cucucuggug aaagugccgc caucuuuuga 60
guguuac 67

<210> 304
<211> 67
<212> RNA
<213> Homo sapiens

<400> 304
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gcgucac 67

<210> 305
<211> 69
<212> RNA
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<400> 305
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ggguguccc 69

<210> 306
<211> 72
<212> RNA
<213> Homo sapiens

<400> 306
uacaucggcc auuauaauac aaccugauaa guguuauagc acuuaucaga uuguauugua 60

auugucugug ua 72

<210> 307
<211> 102
<212> RNA
<213> Homo sapiens

<400> 307
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aagugcugcg acauuugagc gucaccggug acgcccauau ca 102

<210> 308
<211> 101
<212> RNA
<213> Homo sapiens

<400> 308
gcaucccccuc agccuguggc acucaaacug ugggggcacu uucugcucuc uggugaaagu 60

gccgccaucu uuugaguguu accgcuugag aagacucaac c 101

<210> 309
<211> 102
<212> RNA
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<400> 309
cgaggagcuc auacugggau acucaaaaug ggggcgcuuu ccuuuuuguc uguuacuggg 60

aagugcuucg auuuuggggu gucccuguuu gaguagggca uc 102

<210> 310

<211> 22
<212> RNA
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<400> 310
ugagguagua gguuguauag uu 22

<210> 311
<211> 22
<212> RNA
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<400> 311
ugagguagua gguugugugg uu 22

<210> 312
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<400> 312
ugagguagua gguuguaugg uu 22

<210> 313
<211> 21
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<400> 313
agagguagua gguugcauag u 21

<210> 314
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<212> RNA
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<400> 314
ugagguagga gguuguauag u 21

<210> 315
<211> 22
<212> RNA
<213> Homo sapiens

<400> 315
ugagguagua gauuguauag uu 22

<210> 316
<211> 21
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uccgucucag uuacuuuaua gcc 23

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ucucacacag aaaucgcacc cguc 24

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ugcugacucc uaguccaggg c 21

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acauagagga aauuccacgu uu 22

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<212> DNA
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic primer

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<210> 500
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<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic primer

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<210> 501
<211> 23
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<223> Description of Artificial Sequence: Synthetic primer

<400> 501
ccaggagctc aggaagaaga gat 23

<210> 502
<211> 25
<212> DNA
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic primer

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<210> 503
<211> 26
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<220>
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<213> Artificial Sequence

<220>
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<210> 505
<211> 26
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<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic primer

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<223> Description of Artificial Sequence: Synthetic primer

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<210> 507
<211> 31
<212> RNA
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<220>
<223> Description of Artificial Sequence: Synthetic oligonucleotide

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Claims

1. A method of diagnosing or prognosticating cancer and/or a myeloproliferative disorder in a subject, comprising:

   i) determining the level of at least one miR gene product in a sample from the subject; and
   ii) comparing the level of the at least one miR gene product in the sample to a control, wherein an increase in the level of the at least one miR gene product in the sample from the subject, relative to that of the control, is diagnostic or prognostic of cancer and/or a myeloproliferative disorder, and

   wherein the at least one miR gene product is selected from the group consisting of miR-126.

2. A method of treating a cancer and/or a myeloproliferative disorder in a subject, comprising administering to the subject an effective amount of a compound for inhibiting expression of at least one miR gene product, wherein the at least one miR gene product is selected from the group consisting of miR-126.

3. The method of claim 1 or 2, wherein the at least one miR gene product comprises the group consisting of miR- 101, miR-126, miR-106, miR-20 and miR-135.

4. The method of claim 1 or 2, wherein the cancer and/or a myeloproliferative disorder is a cancer.

5. The method of claim 4, wherein the cancer is a leukemia.

6. The method of claim 5, wherein the leukemia is acute myeloid leukemia.

7. The method of claim 6, wherein the acute myeloid leukemia is acute megakaryoblastic leukaemia.

8. The method of claim 4, wherein the cancer is multiple myeloma.

9. The method of claim 1 or 2, wherein the cancer and/or a myeloproliferative disorder is a myeloproliferative disorder.

10. The method of claim 9, wherein the myeloproliferative disorder is selected from the group consisting of essential thrombocytemia (ET), polycythemia vera (PV), myelodisplasia, myelofibrosis and chronic myelogenous leukemia (CML).

11. The method of Claim 1, wherein the control is selected from the group consisting of:

i) a reference standard;
ii) the level of the at least one miR gene product from a subject that does not have cancer and/or a myeloproliferative disorder; and
iii) the level of the at least one miR gene product from a sample of the subject that is non-cancerous and/or does not exhibit a myeloproliferative disorder.

12. The method of Claim 1 or 2, wherein the subject is a human.

13. A pharmaceutical composition for treating a cancer and/or a myeloproliferative disorder comprising an effective amount of a compound for inhibiting expression of at least one miR gene product and a pharmaceutically-acceptable carrier, wherein the at least one miR gene product is selected from the group consisting of miR-126.

14. The pharmaceutical composition of Claim 13, wherein the at least one miR gene product comprises the group consisting of miR-101, miR-126, miR-106, miR-20 and miR-135.

15. The pharmaceutical composition of claim 13, wherein the pharmaceutical composition further comprises at least one anti-cancer agent.

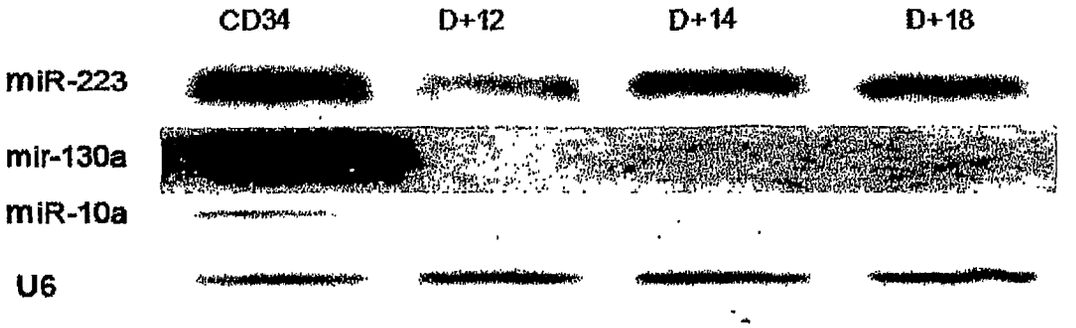


FIG. 1A

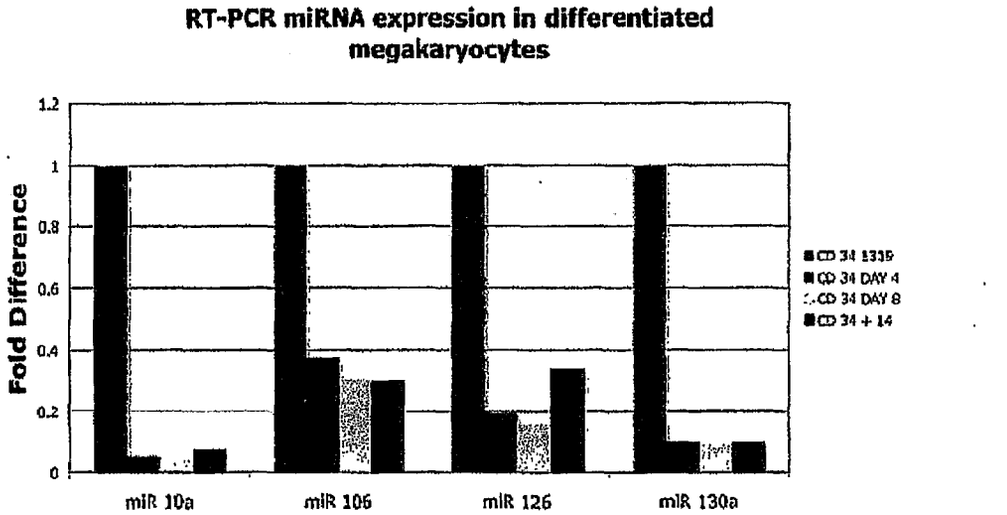


FIG. 1B

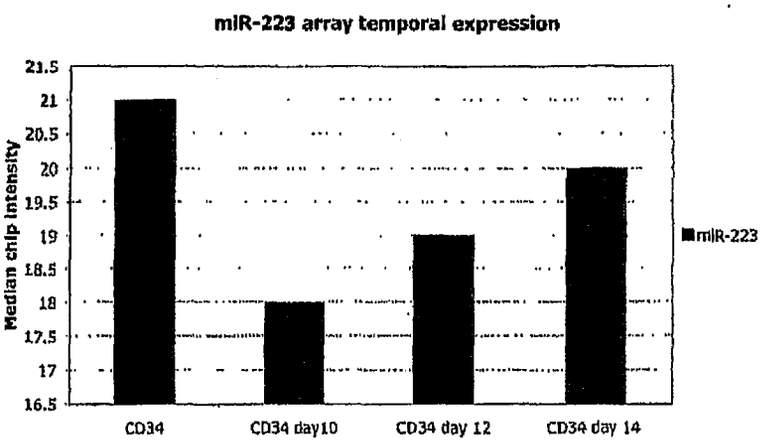


Fig. 1C

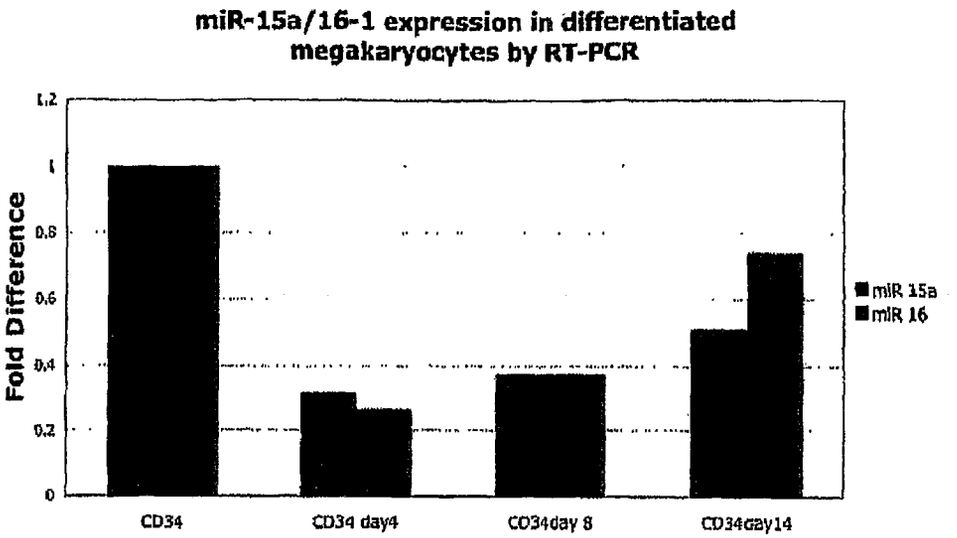

miR-15a/16-1 expression in differentiated megakaryocytes by RT-PCR
Fold Difference
1.2
1
0.8
0.6
0.4
0.2
0
CD34
CD34 day4
CD34day 8
CD34day14
miR 15a
miR 16

FIG. 1D

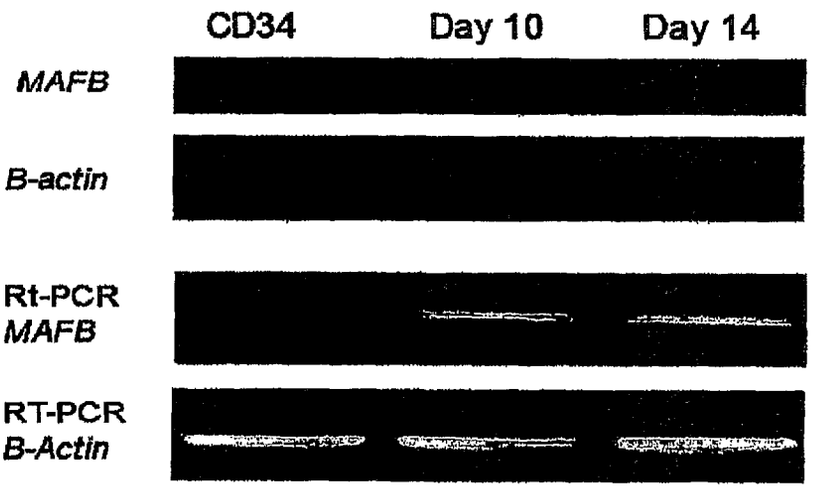

CD34
Day 10
Day 14
MAFB
B-actin
Rt-PCR
MAFB
RT-PCR
B-Actin

FIG. 2A

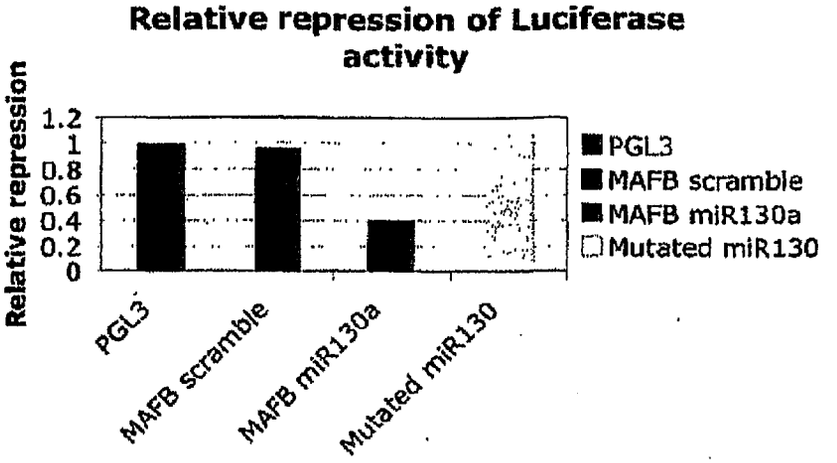


FIG. 2B

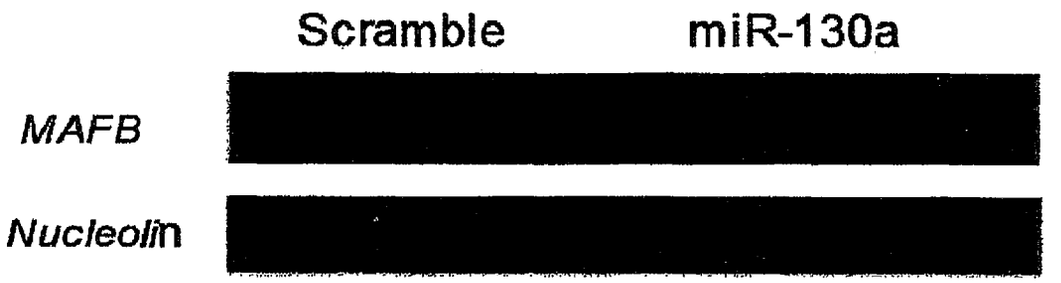


FIG. 2C

HOX A1 GENE EXPRESSION

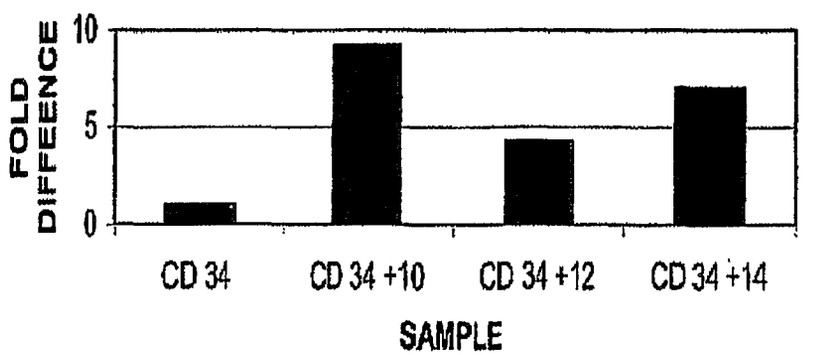


FIG. 3A

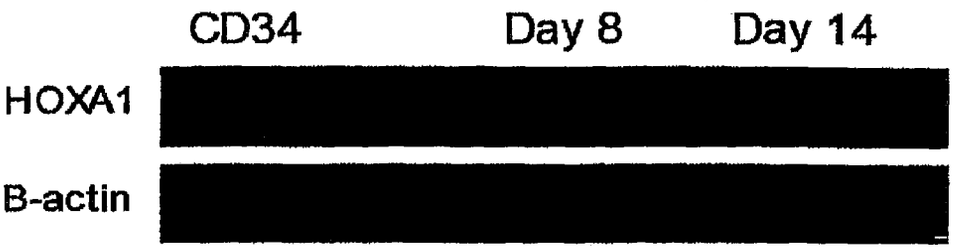


FIG. 3B

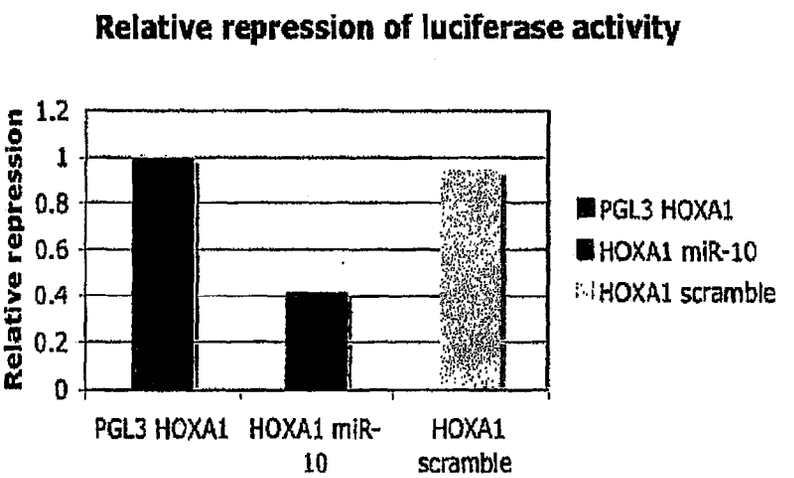


FIG. 3C

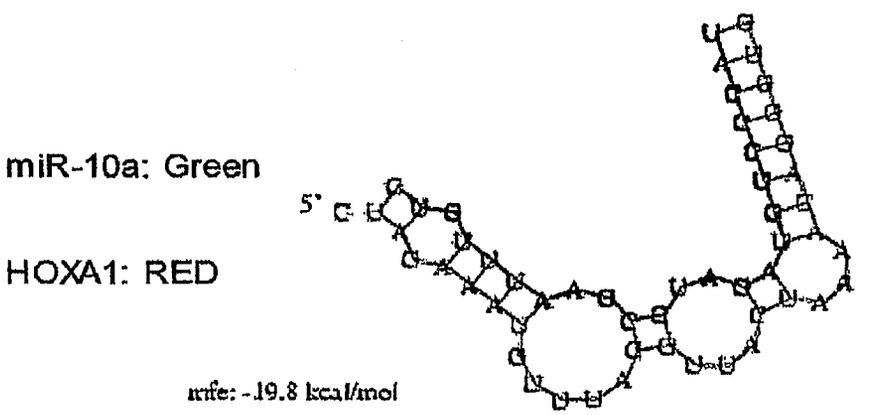


FIG. 3D

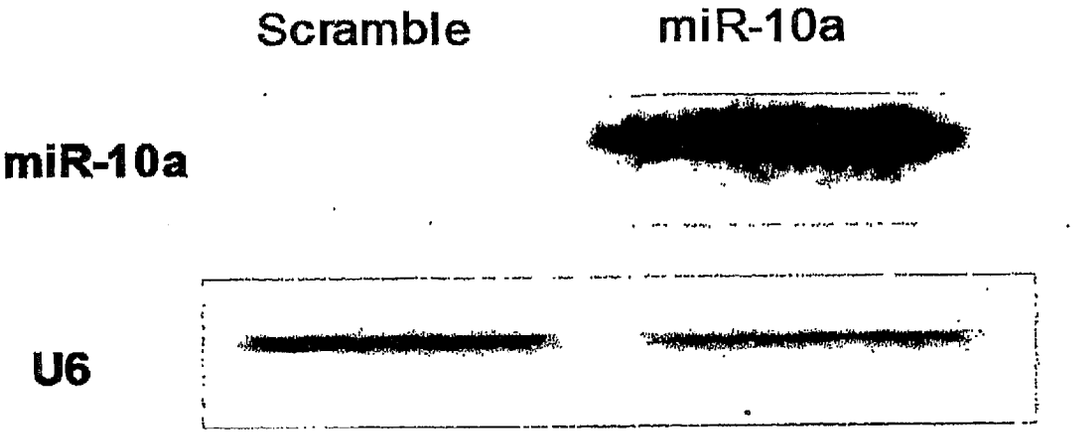


FIG. 3E

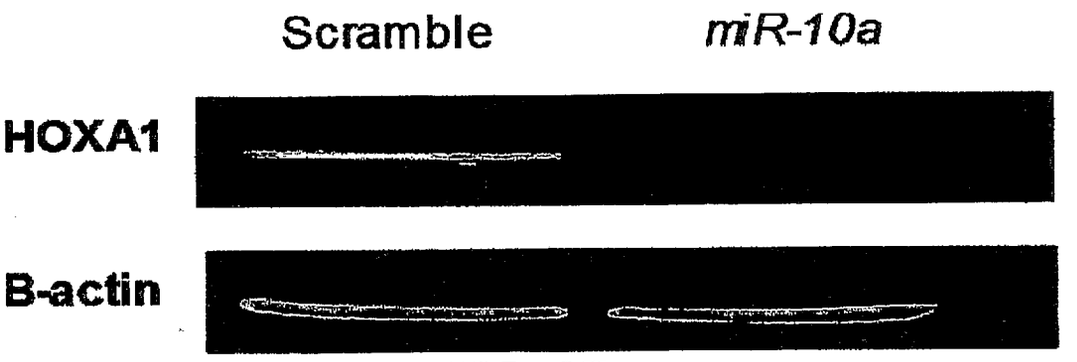


FIG. 3F

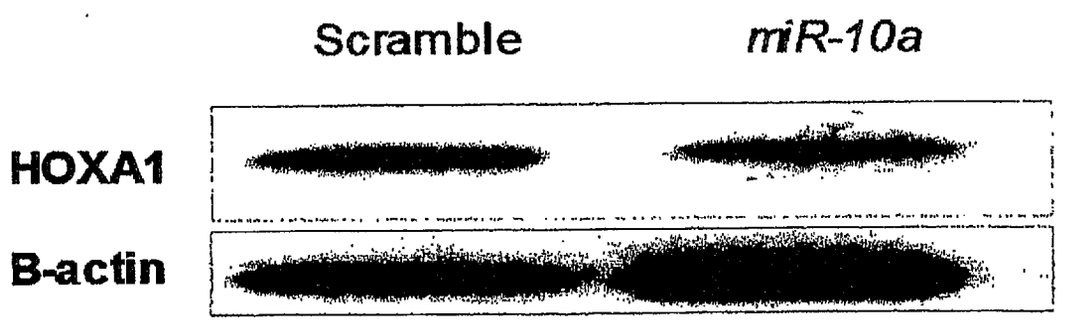


FIG. 3G

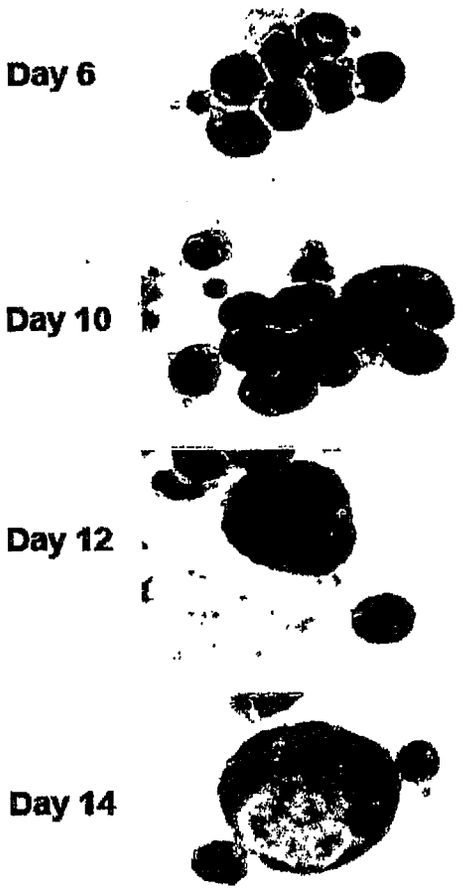


FIG. 4A

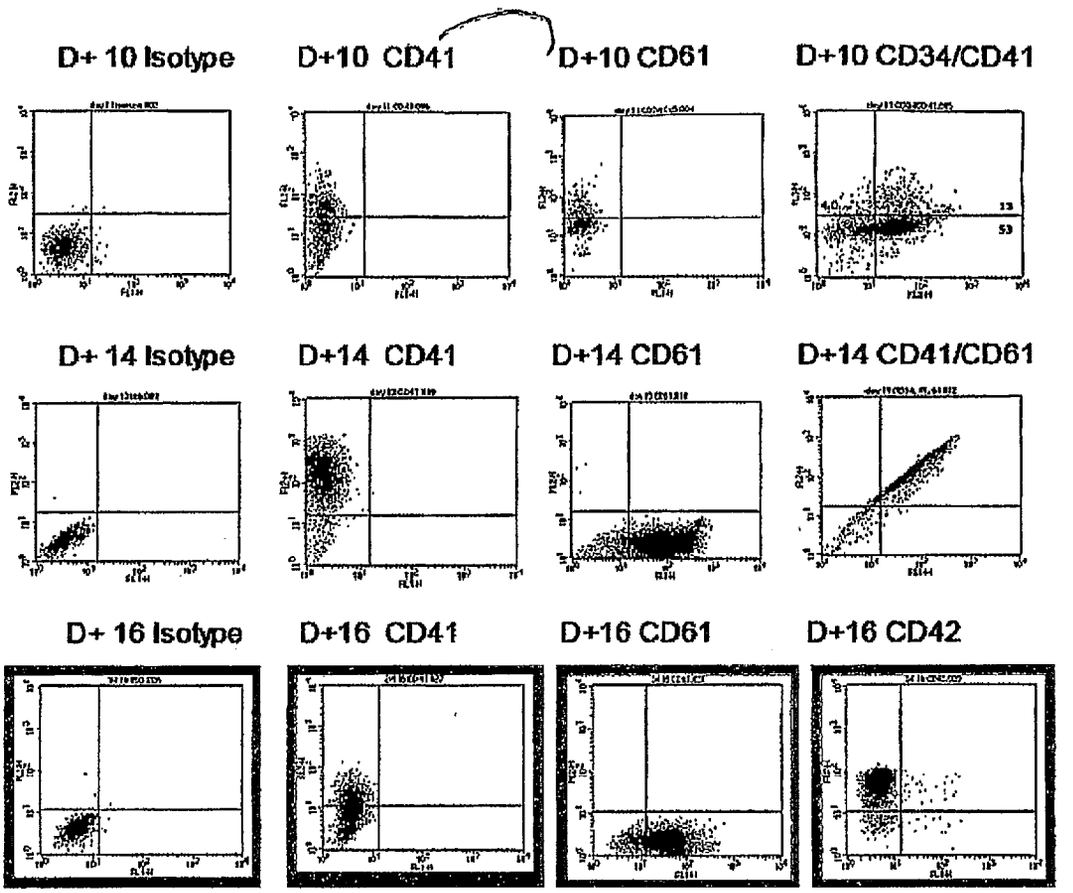

D+ 10 Isotype
D+10 CD41
D+10 CD61
D+10 CD34/CD41
D+ 14 Isotype
D+14 CD41
D+14 CD61
D+14 CD41/CD61
D+ 16 Isotype
D+16 CD41
D+16 CD61
D+16 CD42

FIG. 4B

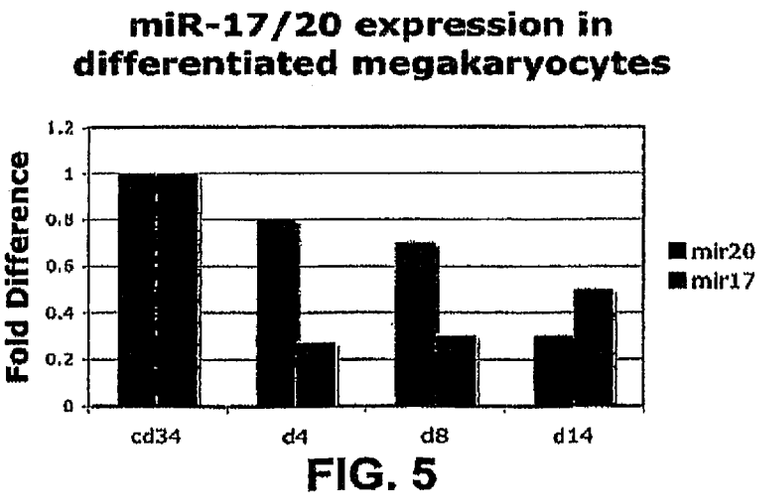

miR-17/20 expression in differentiated megakaryocytes
Fold Difference
1.2
1
0.8
0.6
0.4
0.2
0
cd34
d4
d8
d14
mir20
mir17

FIG. 5

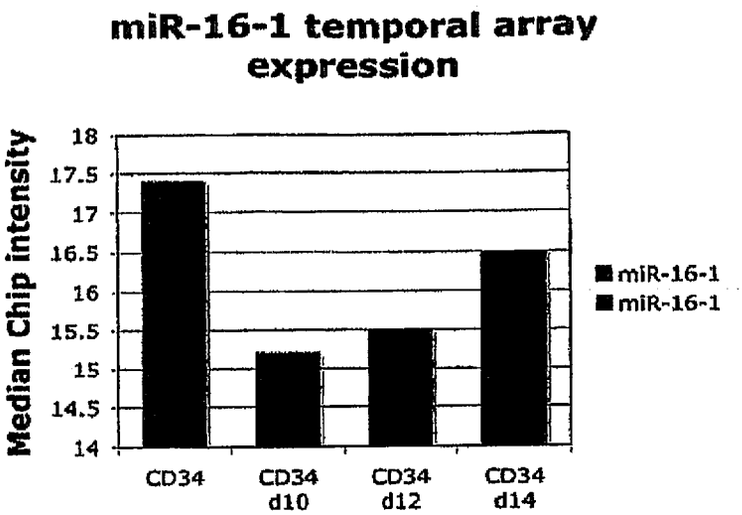

miR-16-1 temporal array expression
Median Chip intensity
18
17.5
17
16.5
16
15.5
15
14.5
14
CD34
CD34 d10
CD34 d12
CD34 d14
miR-16-1
miR-16-1

FIG. 6A

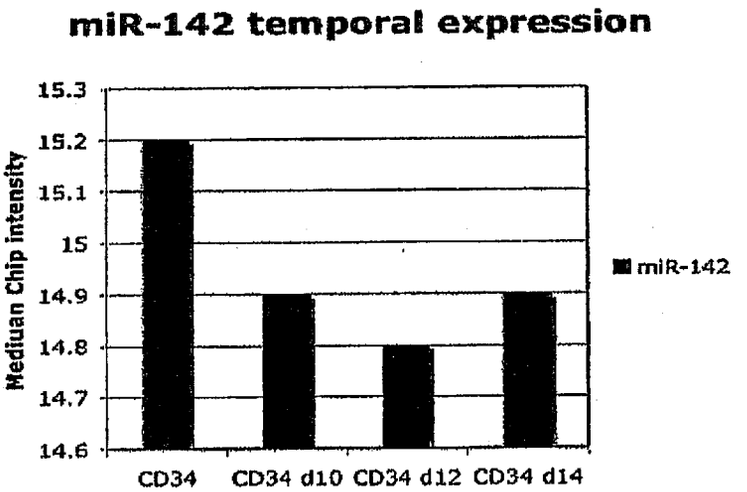

miR-142 temporal expression
Mediuan Chip intensity
15.3
15.2
15.1
15
14.9
14.8
14.7
14.6
CD34
CD34 d10
CD34 d12
CD34 d14
miR-142

FIG. 6B

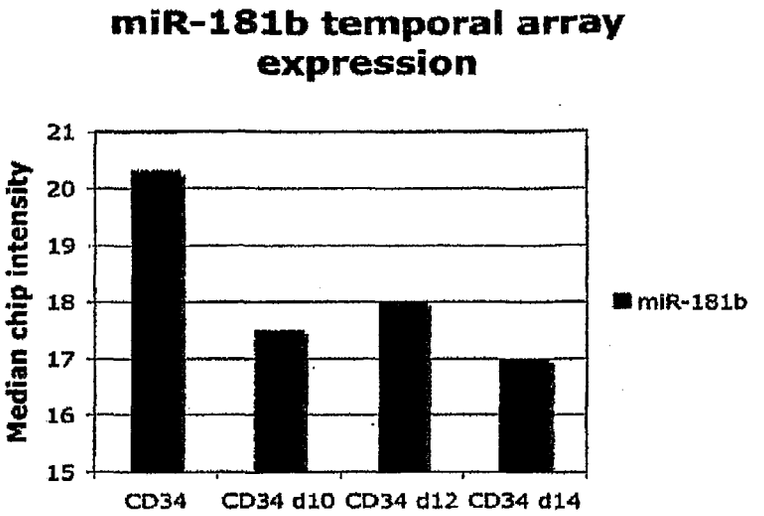

miR-181b temporal array expression
Median chip intensity
21
20
19
18
17
16
15
CD34
CD34 d10
CD34 d12
CD34 d14
miR-181b

FIG. 6C

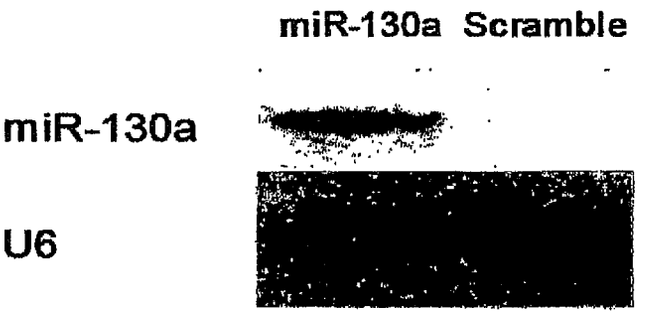
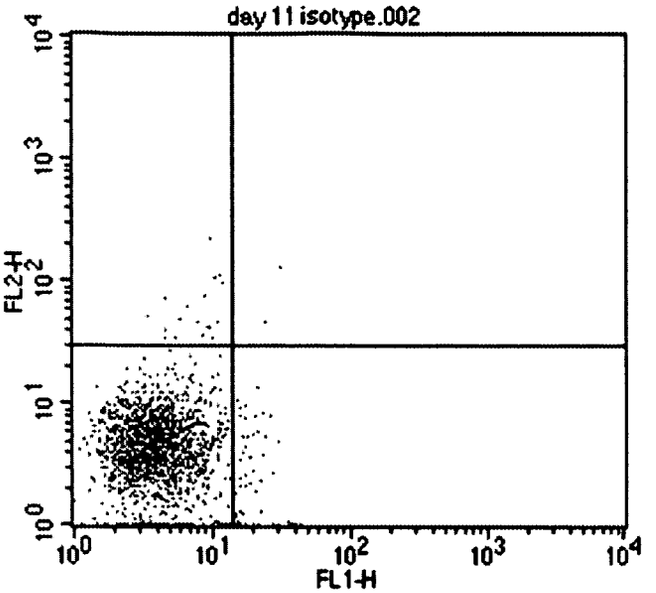

miR-130a Scramble
miR-130a
U6

FIG. 7

D+ 10 Isotype



D+ 14 Isotype

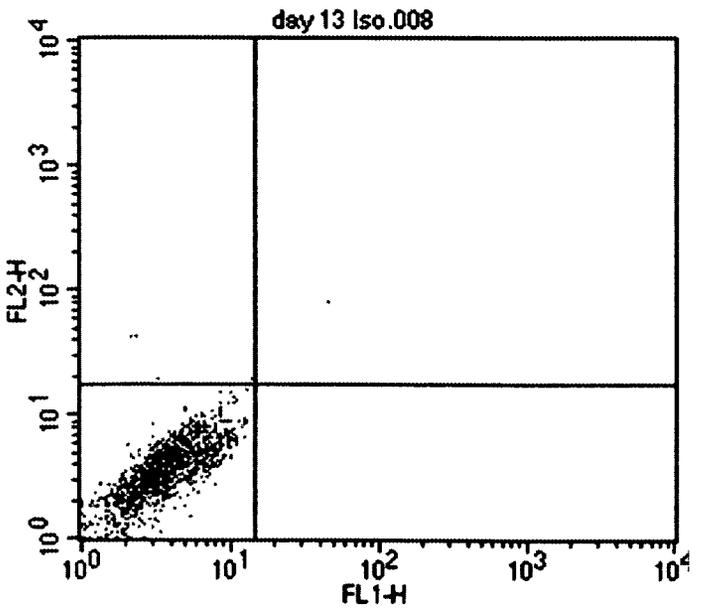
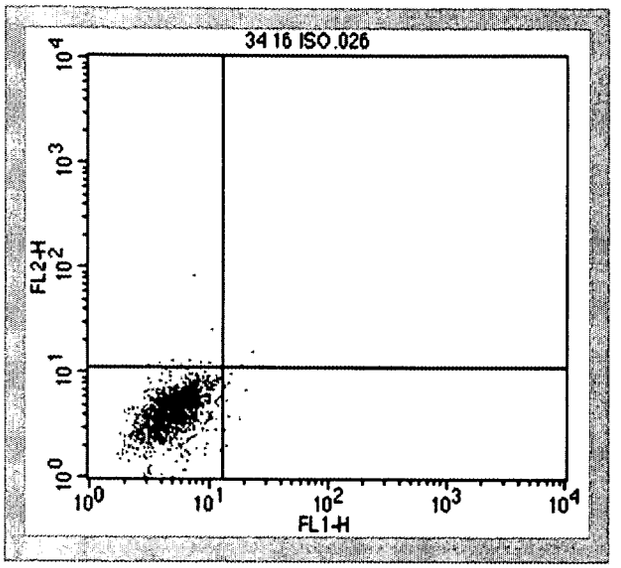


Fig. 4B

D+ 16 Isotype



D+10 CD41

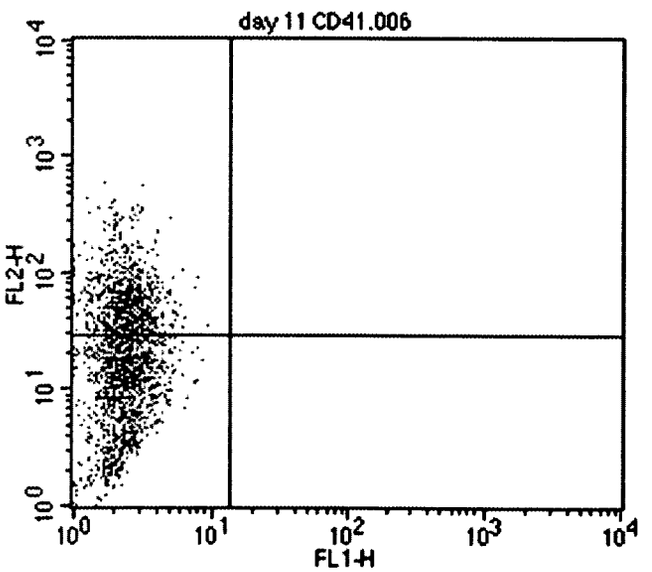
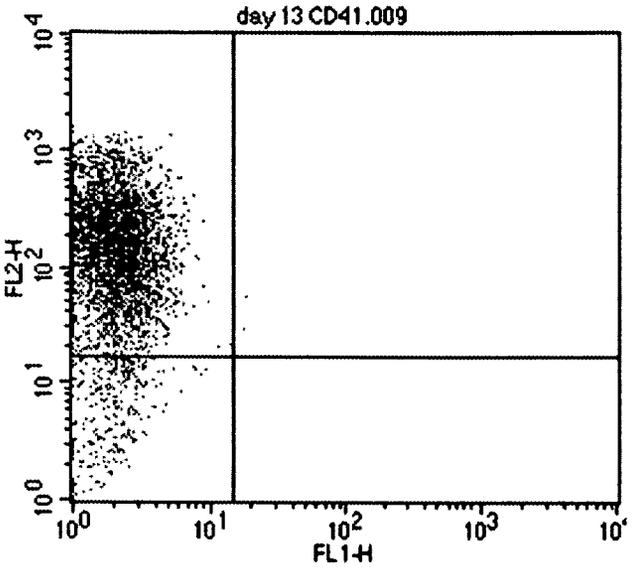


Fig. 4B

D+14 CD41



D+16 CD41

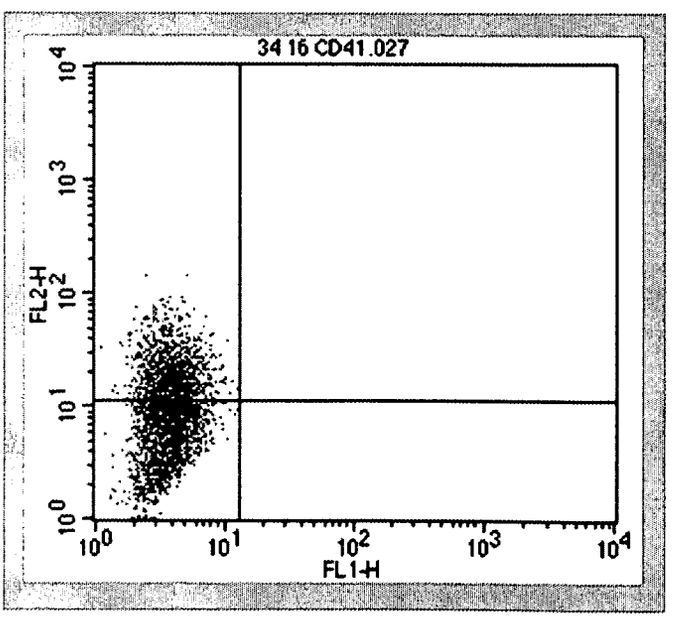
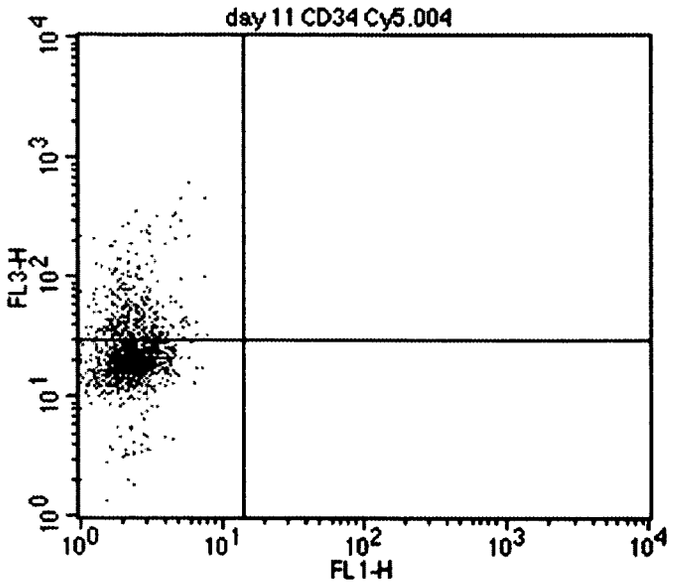


Fig. 4B

D+10 CD61



D+14 CD61

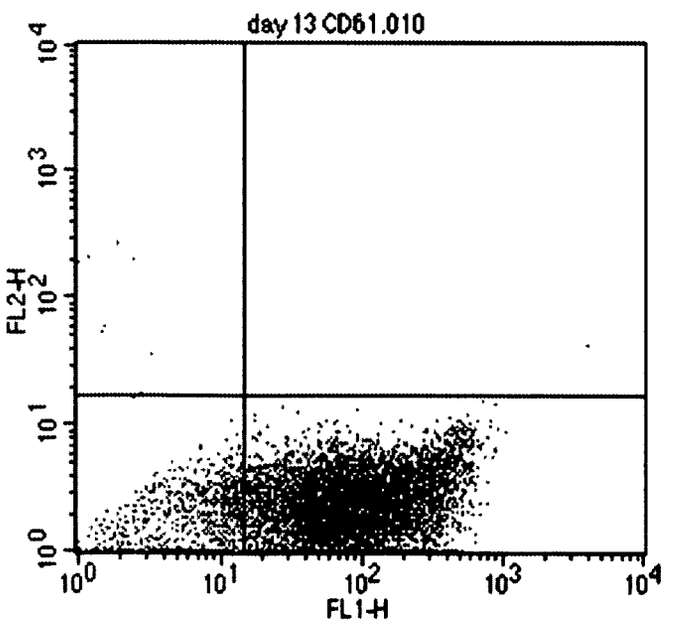
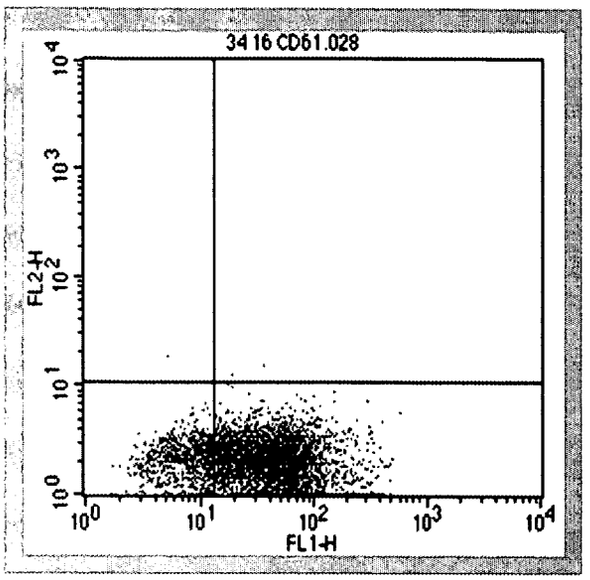


Fig. 4B

D+16 CD61



D+10 CD34/CD41

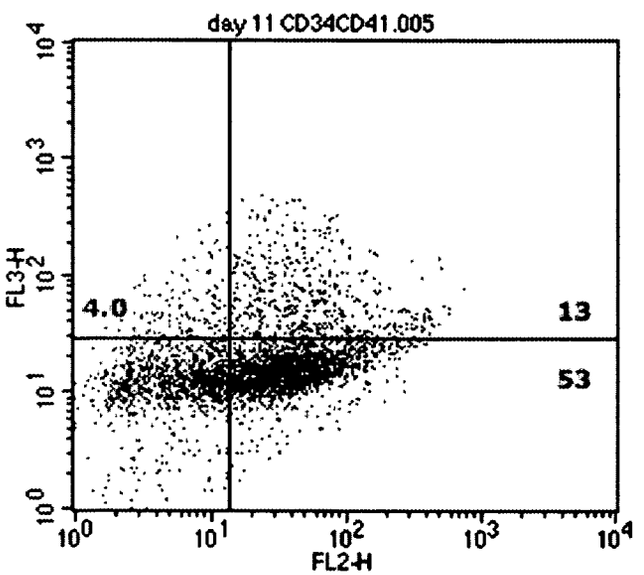
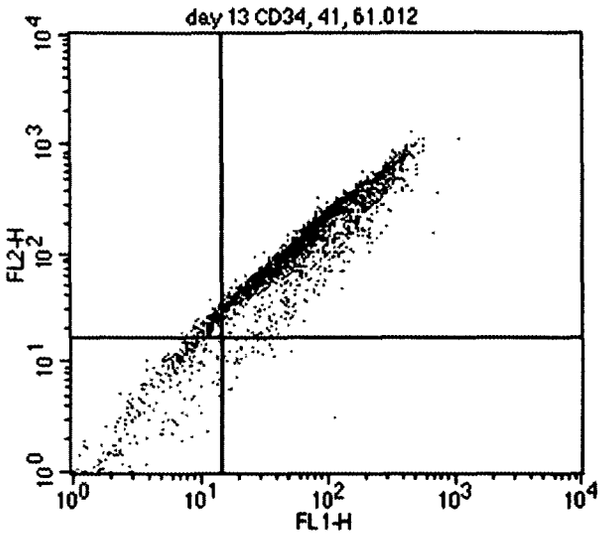


Fig. 4B

D+14 CD41/CD61



D+16 CD42

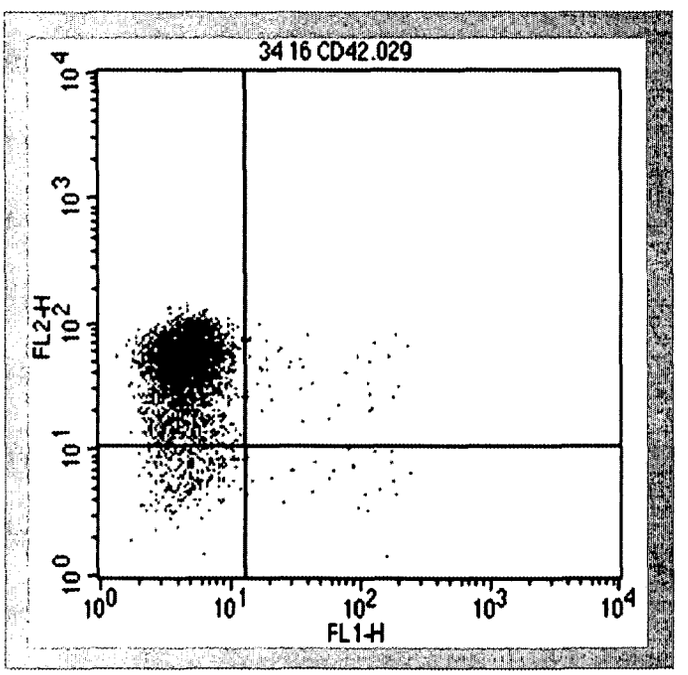


Fig. 4B

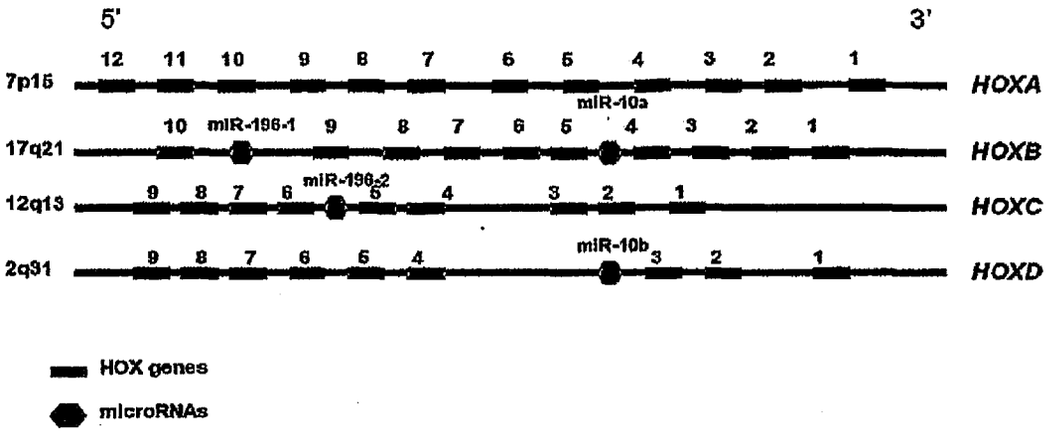

5'
3'
7p15
12 11 10 9 8 7 6 5 4 3 2 1
HOXA
miR-10a
17q21
10 miR-196-1 9 8 7 6 5 4 3 2 1
HOXB
12q13
9 8 7 6 miR-196-2 5 4 3 2 1
HOXC
2q31
9 8 7 6 5 4 miR-10b 3 2 1
HOXD
HOX genes
microRNAs

FIG. 8

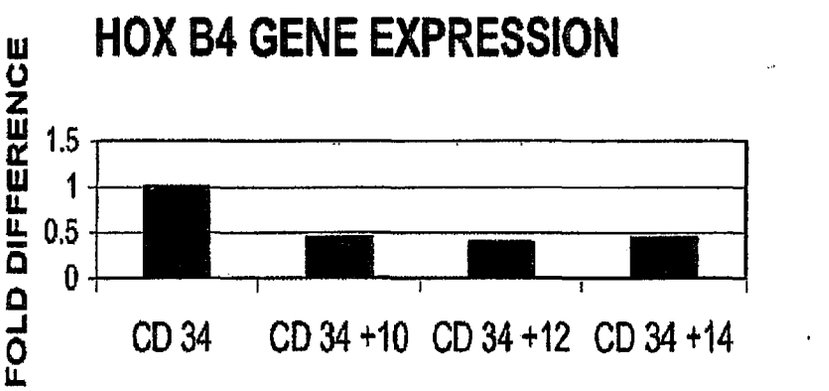

HOX B4 GENE EXPRESSION
FOLD DIFFERENCE
1.5
1
0.5
0
CD 34
CD 34 +10
CD 34 +12
CD 34 +14

FIG. 9A

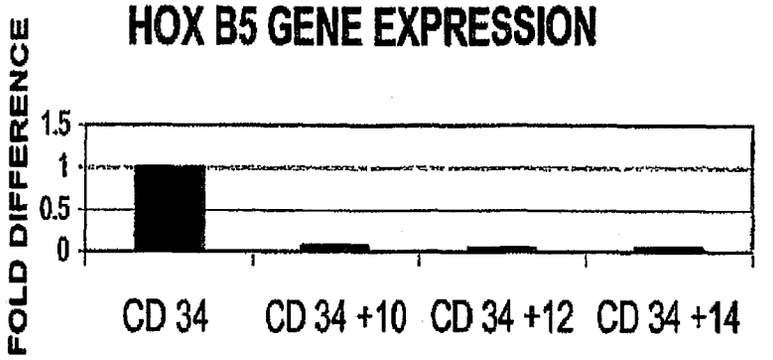

HOX B5 GENE EXPRESSION
FOLD DIFFERENCE
1.5
1
0.5
0
CD 34
CD 34 +10
CD 34 +12
CD 34 +14

FIG. 9B

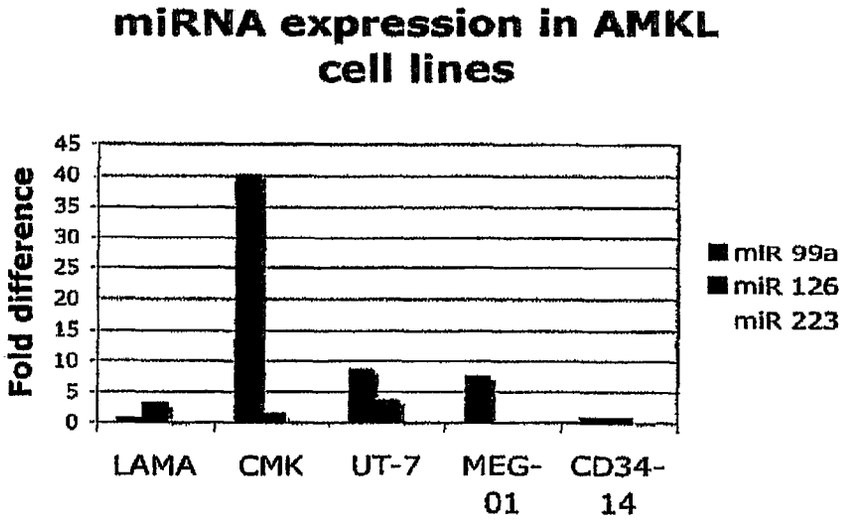

miRNA expression in AMKL cell lines
Fold difference
45
40
35
30
25
20
15
10
5
0
LAMA
CMK
UT-7
MEG-01
CD34-14
miR 99a
miR 126
miR 223

FIG. 10

Europäisches Patentamt
European Patent Office
Office européen des brevets

EUROPEAN SEARCH REPORT

Application Number
EP 11 15 1749

DOCUMENTS CONSIDERED TO BE RELEVANT

Category	Citation of document with indication, where appropriate, of relevant passages	Relevant to claim	CLASSIFICATION OF THE APPLICATION (IPC)
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The present search report has been drawn up for all claims

Place of search	Date of completion of the search	Examiner
Munich	8 July 2011	Sauer, Tincuta

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EUROPEAN SEARCH REPORT

Application Number
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